AYURVEDA AND MODERN MEDICINE

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Matru Devo Bhava, Pitru Devo Bhava, Acharya Devo Bhava

DEDICATION

To the memory of
my mother – Laxmibai (Kaku),
my father – Dattopant (Anna),
and
Charaka, Sushruta & Hippocrates

FOREWORD

Bharatiya Vidya Bhavan has always been in the forefront for upholding the traditional values of life and culture of this great country. Dr. R. D. Lele, an eminent physician actively involved in the development of nuclear medicine in this country, has joined these efforts by bringing out this book on 'Ayurveda and Modern Medicine' as a part of Bhavan's project on 'Ancient Insights and Modern Discoveries'.

Ayurveda has been practised in this country from time immemorial and has stood the test of time. Dr. Lele has methodically gone through the ancient literature of Ayurveda and has taken pains to establish its link to modern medicine on scientific basis. In fusing the concepts of these two disciplines, he has brought out the relevance of physics, chemistry and mathematics in medicine. After all, if the cure of Ayurveda is authentic it must fall into place with the medical sciences. No system can remain static and it must take into note the newer discoveries of science.

With the present level of sophistication in science and technology, medicine does not any more stand isolated as an independent discipline. There is strong and necessary interaction between medicine and life sciences on the one hand and physics, chemistry and mathematics on the other. The discovery of X-rays and radioactivity are important milestones in the development of medical sciences. As rightly pointed out by the author, the scientists and engineers have played significant roles in the development of EEG machines, linear accelerators, RIA techniques, CT scanners, ultrasonic and NMR imaging. The concept of treating the disease is gradually giving way to that of treating the patient, as has been the basic philosophy of Ayurveda. In this context, the necessity to understand the biomedical and physico-chemical aspects of the patient's body and mental functions becomes a significant factor.

In this book the author deals with the body's internal environment, its control systems, the built-in safeguards against diseases and injury.. Thirst and hunger are looked upon as natural urges to offset water and energy losses. The natural defences of the body, whether on the basis

of immunology or the ancient *'Vyadhikshamatva'* are essentially the response functions of the human body as host environment to specify antibody's onslaught. This mechanism is nothing but an efficient defensive action of a bank of 'memory cells' against this aggression. Another hypothesis of modern physiology is the concept of 'margin of safety' that is built-in in the storage of carbohydrates, fats and proteins in the body tissues. Changes in elemental concentration in serum, cardiovascular pressure, water and blood losses, pulmonary functions etc., are duly taken care of by these margins in the human system to preserve health.

The book rightly dwells on the concept of 'mind as an abode of a healthy body' as propounded by Charaka. The body functions covering reflex action, pleasure, experience, psychosomatic disorders, mental aberrations, reactions to stimulants, etc., are all explained as the interaction of mind and body. The mental illness and behavioural pattern of human beings are two important fields of study, both in *Charaka Samhita* and modern psychology, even though the technical approaches in the two systems may be different.

An important chapter is rightly devoted to the health effects (physical and mental) on man, by factors such as tobacco, alcohol and drugs. Among the prescriptions to ward off these social problems is the practice of yoga advocated in a forceful manner.

Pharmacology and toxicology, both modern and ancient, are explained in a lucid fashion and it can be seen how some of the new drugs have their genesis in the herbarium of the ancients.

Dr. Lele has also traversed through the exotic topics, such as ageing, rejuvenation of the elderly, virilification therapy or vajikarana, psychology of sex and the concept of *brahmacharya.* Hygiene and public health rightly take a very important position in modern life and their significance has been well brought out.

In his earlier book on the 'Principles and Practice of Nuclear Medicine', Dr. Lele tried to address the medical community; in the present book he endears himself to the ordinary reader who is not a scientist or a practising doctor.

RAJA RAMANNA

PREFACE

Bhavan's Ancient Insights and Modern Discoveries (AIMD) Project, which was inaugurated at an exploratory symposium has for its objectives the utilisation of Ancient Indian Insights for co-relation, linking and synthesis with modern scientific discoveries. The Project functions through its three divisions namely, Science and Technology, Life and Health Sciences and the Centre for Synthesis of Science and Spirituality.

In the Life and Health Sciences Division, one of the research assignments was a comprehensive monograph on Ayurveda and modern medicine. We felt that such a monograph would enlighten practitioners of modern medicine with insights of Ayurveda and the Ayurvedic physicians with modern achievements. I considered Dr. R. D. Lele to be the most competent person to take up this job.

Dr. Lele worked on the project, assisted by his wife Mrs. Lele, who helped him with the collection, collation etc. of the relevant literature. There were also several periodical meetings at which the assignment was discussed and assistance from other Researchers was made available. Dr. Lele completed the assignment and the monograph has now been printed.

It has been written from a rigidly critical and scientific point of view and as such is bound to find favour with the modern scientific community. Despite its critical tenor, the insights of ancient medicine stand out prominently justifying the oft-quoted dictum

"Dagdham Dagdham Punarapi Punah
Kaanchanam Kaanthavarnam"

"Gold acquires again and again its lustrous quality
in spite of repeated melting through fire".

Dr. Ramchandra Lele was born in 1928 in Hyderabad City, where he graduated in 1949 from the Osmania Medical College. After doing rural medical service in the former State of Hyderabad for 5 years, he went to England in 1955 for higher studies in medicine. On his return in 1957, he joined the full-time teaching cadre of Maharashtra State. He has been Professor and Head of the Department of Medicine at Aurangabad, Nagpur and Bombay. In 1972, he became the Dean of the Grant Medical College and Sir J.J. Group of Hospitals, Bombay. In July 1973,

I invited him to join the Jaslok Hospital and Research Centre as Chief Physician and Chief of Nuclear Medicine, the position he continues to hold till today. An eminent physician, he has attained the status of a super-consultant who practises scientific and humane medicine.

Dr. Lele is a pioneer in Nuclear Medicine in India. His book "Principles and Practice of Nuclear Medicine", published in 1984, has been acclaimed by eminent experts abroad as "outstandingly good".

As the Dean of Grant Medical College and J.J. Hospital he demonstrated great dynamism and initiative in getting things done, cutting through bureaucratic red-tape and inertia. Dr. Lele has been active in the Hospital Management Conferences in India and has written and spoken extensively on medical audit, cost-benefit analysis, quality assurance, computerization in hospital management etc.

He is widely known as an excellent teacher in Medicine, both for undergraduates and post-graduates. The clinical museums he created at the Nagpur Medical College and Grant Medical College, Bombay have been unique. He is currently engaged in pioneering computer-assisted instruction in medicine and computer-assisted medical decision-making in India.

Dr. Lele has given several prestigious orations on medical subjects in different parts of India, and has been a very popular speaker at various conferences, symposia and refresher courses for medical practitioners.

The late Pandit Shiv Sharma, the doyen among Ayurvedic physicians in India and S.E. Asia, had publicly praised Dr. Lele as a "modern physician with an Ayurvedic outlook".

We hope that the publication of this book will create a new climate of understanding for both Ayurveda and modern medicine and help them to come closer together to understand each other so that a more wholesome and integrated system of health care and maintenance could be ushered in.

The Bhavan is grateful to Inland Printers for the neat and expeditious printing of the book.

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Bombay
February 18, 1986

INTRODUCTION

Ancient India looked upon life as an integrated whole taking all knowledge in its purview. The intuition of our Rishis covered many fields – astronomy, atomic theory, mathematics, botany, medicine, philosophy, etc.... The Bhavan's new project 'Ancient Insights and Modern Discoveries' is an earnest attempt at exploring the possibilities of a meaningful correlation between the ancient insights – intuitive discoveries – of India's seers and saints and modern scientific discoveries and technological achievements ..... To my mind, this is one of the most significant projects ever undertaken in this country.

– Jayaprakash Narayan

India, as a nation, is currently fragmented into three large groups. The first group, cherishing the ancient values, holds on to the heritage and religion, with almost ancestral vainglory. The second group, highly influenced by the Western culture and technology, is quite keen for a rapid commercial exploitation of our resources. This group is quite visible, articulate and indulges in "scientism". And the last group – a vast, apathetic majority, worried about their daily bread and necessities of life, looks on in a perplexed manner to the harangues of politicians asking them to rapidly move on to the twenty-first century and to the endless religious discourses of all *Gurus,* and *Bhagwans,* reminding them of *Maya* and the utmost need of salvation.

Without any implied value judgement, it is obvious that there are overt and covert psychological determinants for such partisan views. A civilization, with a continuity of thousands of years, when faced with the marvels of modern science and technology, has several options. The first option, an easy ostrich-like one, in a nation with massive illiteracy, is to claim and proclaim that our sages, saints and Yogis knew it all. As a consequence, a special kind of delusion got widespread – the Germans, the British and others stole our valuable manuscripts in Sanskrit, which had all these secrets of science! Some of the protagonists of 'Shuddha Ayurveda' and their political supporters opt for such a view. In contrast, a large number of doctors, chemists, engineers, physicists, molecular biologists, computer experts, etc. are

so impressed with the prowess and the pace of the modern technology that they tend to ridicule the ancient knowledge and even those who seek to investigate it scientifically.

The two options of ancestral vainglory and a chauvinistic attitude to the Western technology do not exhaust all the options available to us. The Bhavan sensed the need for a third option – to scientifically explore the correlation of ancient insights and modern discoveries (AIMD). Two conferences have been held in the past, when many scientists and scholars, who tend to share such an option, gathered and communicated effectively. This generated an intensely charged climate of anticipation and hope for novel research projects in the fields of Science and Technology and in Life and Health Sciences.

Prof. R. D. Lele participated in the AIMD symposium organised at New Delhi in 1978, by Bharatiya Vidya Bhavan. We appreciated his critical attitude and a certain amount of reluctance. These qualities were expected in a medical teacher and a pioneer in nuclear medicine in India. Earlier, while Dr. Lele and myself were once actively debating the need to conduct research in Ayurveda, our mutual friend Dr. Arun S. Namvadekar amusedly looked on at our wordy duel. He remarked with philosophical placidity, "Ashok! you ought to learn the skills of persuasive communication." Later, in 1979, Prof. Lele was instrumental in persuading the Bhavan that a team be sent to attend an International Conference on 'Traditional Asian Medicine', held at Canberra, Australia. The conference provided a forum for interesting scientific presentations and discussions. The Bhavan then decided, at the behest of Dr. Shantilal J. Mehta, Honorary Chairman of Life and Health Sciences (AIMD), that Prof. Lele's proposed monograph on 'Ayurveda and Modern Medicine' be sponsored. Seven years after that wise decision, the present volume by Prof. R. D. Lele bespeaks the path he has travelled, enjoyed and made beckoning to others – Ayurvedic and modern practitioners and students alike.

An enthusiast for the modern medicine and a medical teacher of renown, Prof. R. D. Lele studied *Vriddha-Trayi* (Charaka, Sushruta and Vagbhata) and debated the subtle points of several sutras with late Dr. P. J. Mehta, Acharya Antarkarji, Vaidya Suresh Chaturvediji and many others. He selected aphorisms from Ayurveda, akin to the aphorisms of Hippocrates and attempted to cover the diverse aspects of modern medicine and basic science, in relation to these aphorisms. The result has been a sizable and fairly encyclopaedic ensemble of the ancient and modern medicines. It is hoped that the book will serve as a bridge rather than as a wall. One is reminded of a couplet from Robert Frost:

Before I build a wall, I'd ask to know
What I was walling in or walling out.

We have too many walls in our culture, what we need are bridges of communication and cooperation, across the chasms of polarity of views and attitudes.

In the present introduction to this volume, I will try to identify the functional linkages between Ayurveda and modern medicine, which offer potential for well-planned biomedical research. It would be presumptuous on my part to attemp to be exhaustive. It is always difficult to prophesy in science. It is also not easy to develop new knowledge from old wisdom. However, we ought to bear in mind what Robert Oppenheimer said, "Both the men of science and the men of art live always at the edge of mystery, surrounded by it; both, always as the measure of their creation, have had to do with the harmonization of what is new with what is familiar, with the balance between novelty and synthesis, with the struggle to make partial order in total chaos .... They in their work and their lives, help themselves, help one another and help all men".

The very first chapter of the book – 'Aurveda through Modern Eyes' – offers a feast of pithy aphorisms loaded with wisdom. Aphorisms—like Zen Koans – continue to offer opportunities for deep thought and meditation. Not a direct transfer of information but a stimulus to thinking in depth was the objective of our ancient teachers, who revelled in Sutras. A comparative historiography of the aphorsisms from Charaka, Hippocrates, Shen Nung, Avicenna, etc. may provide an excellent opportunity for AIMD research.

For example, Charaka has stated:

Traya upasthambha Ityaaharah Swapno Brahmacharyamiti
Ebhistriyuktena Yuktairupasthabdhamupasthambhaih Shariram
Balavarnopachayopachitamanuvartate Yavadayuh Samskarat.

"The healthy life has three main pillars – a balanced diet, proper sleep and a healthy sex life and mental hygiene".

Sushruta also defines a healthy person as:

Samadoshah samaagnischa samadhatumanashrayah
Prasannatmendriyamanah swastha itayabhidhiyate.

"One whose doshas, agni, body elements and excretory functions are harmonious and whose self, mind and senses are cheerful – he is said to be healthy." The emphasis on homeostatic harmony in Ayurveda is a very wholesome and holistic concept. The harmony of the plant and animal life was also stressed. Certain general *shodhana*

procedures are prescribed to restore the homeostatic balance. It is necessary to identify the physiologic, biochemical and clinical correlates of the homeostatic balance induced by *shodhana*. A research project can be carried out on the effects of Panchakarma procedures on hormonal profiles, metabolic markers and immune status of the patients, in addition to the global clinical scores for improvement. It has been proposed to initiate such a project, under AIMD, at Swami Prakashananda Ayurvedic Hospital and Research Centre, Juhu in collaboration with International Institute of Ayurveda, Coimbatore.

The patient's own responsibility and commitment to getting well has been emphasized in Ayurveda. Educational programmes for patients and the community can lead to a better compliance and a speedy recovery. For the chronic diseases like diabetes mellitus, hypertension, bronchial asthma, coronary heart disease, cancer, rheumatoid arthritis, skin allergy, etc. it is desirable to initiate patient-group discussions, Audio-visual media and reading materials can also be gainfully employed. Such a strategy has already paid rich dividends in the management of hypertension, gout, diabetes, cancer detection, etc. AIMD's Life and Health Sciences Division has already initiated educational programmes for the common gastrointestinal diseases. Ayurvedic and modern physicians can meaningfully participate in a co-operative endeavour for such patient and health education.

'Vata', 'pitta' and 'kapha' are considered to be still relevant to their practice by Ayurvedic experts. Modern medicine, having abandoned the humoral theory, has chosen anatomic and pathophysiologic changes as the frame of reference for diagnosis and therapy. Currently, no correlates of 'vata', 'pitta' and 'kapha' are of the parlance of in modern medicine. And not much relevant and validated research has been carried out in 'Tridosha' theory, notwithstanding Dr. K. N. Udupa's attempts to categorize on the basis of neurohumoral transmitters. Prof. Lele has also avoided opening this Pandora's box. He finds the concept of *Dhatu Samyakriya* close to the modern concept of homeostasis, but he clearly has no interest in stretching the concept of 'kapha', 'vata' and 'pitta' as "physico-physiologico complex". He would rather drop these terms altogether.

The vicarious sense of mastery that man gains by naming and classifying the objects in the environment, would almost rechristen *Homo sapiens* into *Homo classificans*. All attempts to classify must be visualized as pragmatic guidelines for handling reality. Whether 'vata', 'pitta' and 'kapha' offer a practical frame of reference to current practitioners of Ayurveda, notwithstanding the modern taxonomy of diseases, has to be scientifically studied. The most difficult aspect of interaction

between the two systems of medicine is the basic difference in the philosophical substratum – *Sankhya* in Ayurveda and molecular reductionism in modern medicine.

One was always intrigued during the premedical courses that mathematics was considered to be vital for aspirant engineers but not for the prospective physicians. Precise measurement is one of the chief components of scientific research. Prof. Lele has tried to correlate the concepts of measurement in Ayurveda and modern medicine. It must be made mandatory to use metric weights in Ayurveda. The ancient and medieval system of standard weights in India needs to be carefully studied. As Vaidya Antarkarji informs me, there are often marked discrepancies between the doses of Ayurvedic drugs in ancient text books and those in current practice. This needs to be investigated. Dose-searching, rigorous, human pharmacologic studies with effective Ayurvedic drugs are essential.

Mathematics and statistics relevant to biomedical sciences must be part of the curriculum for all medical students during their training. They must learn the art of reasoning with statistics, calculus, vectors, Boolean algebra systems and the theory/role of computers in medicine.

Chronobiological and chronopharmacological considerations in health and disease are being intensely investigated. Franz Halberg has been one of the pioneers in this field. The circadian and ultradian rhythms have been studied for hormones, electrolytes, enzymes, etc. It is very essential to understand the synchronizer scheme and the mean cosinor method for chronobiology. Some of these methods can be gainfully employed in studying the effects of certain 'Vardhaman-prayogas' in Ayurvedic as well as for 'Kuti-praveshik Kayakalpa'. The specific instructions of dosing at particular time of the day, particular season etc. will have to be carefully calculated from such an angle. A clinical pharmacology unit can actively collaborate in such a research effort.

A pioneer in nuclear medicine, Prof. Lele is naturally enamoured of the breath-taking advances in modern physics – particularly the health technology and instrumentation at our disposal. The Table in the monograph showing a formidable list of biomedical technology would impress any person. However we have to weigh and balance the cost and effectiveness of high technology in medicine. Biomedical engineering has to be actively cultivated as a discipline, to adapt and evolve appropriate technology for health services in India.

The computer revolution in medicine has been duly emphasized by Prof. Lele, who himself is pioneering this field in India. Our computer

experts are some of the best in the world. The hospital and clinic computers can be cost-effective in terms of adequate data storage and a ready retrieval. The data on indigenous medicinal plants and on drugs used in Ayurveda are already being stored in data bank for meaningful initiation of research projects. We have also initiated a child health project by computer-assisted survey and analysis. AIMD intends to take this up further.

The excitement and activity in the field of molecular basis of pathogenesis have fired the imagination of many biomedical scientists. In the chapter on 'the Chemistry of Life', Prof. Lele has tried to recapture the spirit of this on-going revolution in new biology. Molecular biologists have themselves mutated into diverse species – genetic engineers, gene chemists, gene expression specialists, gene control experts, oncogene biologists, etc. The field is teeming with practical investigations too. A sound chemical background is now essential for medical sciences.

The chapter on "human genetics – ancient and modern", is one of the highlights of this monograph. Sizable information is presented in a lucid and readable form. Ayurvedic and other physicians, who are unaware of the modern genetics, stand to gain by its perusal. Prof. Lele has in a Herculean effort, tried to trace the exciting research in genetics – leading to the current possibilities of a cure of gene-defect diseases. Gene splicing or recombinant DNA research is considered to be analogous to the nuclear fission in physics.

One aspect worth mentioning is the possibility of plant tissue cultures and selective cloning for the high-yield strains. There are many Ayurvedic herbs and plants whose unpredictable therapeutic action is due to low and variable concentrations of the active principles. Some of these species are also scarce. Selection and propagation of the standardized high-yield plants and herbs may reduce such variable drug response. AIMD can initiate such a project of tissue culture of the important medicinal plants. Modern science of nutrition, historically speaking, started as an offshoot of the disorders of vitamin deficiency. On the contrary, Ayurvedic principles and practice of diet are closely linked with the humoral theory and constitutional types of patients. The three gunas and diet have also been correlated in 'Bhagvad-Gita'.

Ayuh Satwabalaarogyasukhapriti vivardhanah
Rasyah snigdhah sthira hrdya Aaharaah satwikapriyah

"The food articles favoured by 'Satthwik' people are juicy, unctuous, palatable, digestible and such articles lead to longevity and an increase in sattwa, energy, health, happiness and love." In contrast,

the currently popular food items – hot, spicy, salty, etc. – are considered favourite of 'Rajasik' persons. These articles lead to misery, sadness and diseases. In an earlier study, we had shown that common salt has a relationship with increased gastric acid secretion, leading possibly to peptic ulcer. Charaka has also related salt with hyperacidity. The relationship of common salt to high blood pressure is well demonstrated by Dahl and others. Hypertension and peptic ulcer are considered to be the common diseases of high-flying business executives – mostly 'Rajasik' individuals.

The effects of foods on brain functions can be an interesting research project for AIMD. There may be a significant role of the precursors of neuro-transmitters in the diet. The varying concentrations in diet of phenylalanine, tyrosine, L-dopa, tryptophan and other aminoacids may influence mental health. Does aging brain require more of these precursors? What are the dietary articles of very healthy aged persons in India? How about their meal habits? These questions can be meaningfully addressed in a research survey.

Goitre has been mentioned in Ayurvedic literature for centuries. Was it reported more in books written in Himalayan region as compared to those originating in the southern India? A comparative study of the ancient manuscripts may provide quite interesting data about iodine-deficiency thyroid diseases.

Food interactions is another area very much emphasized in Ayurveda. We are aware in modern medicine, of drug and food interactions but we have no concept of food-food interactions. Rationally speaking, it is quite plausible for different biochemical constituents to interact in the gastrointestinal tract. The myth and the reality of widespread beliefs on incompatible foodstuffs have to be critically assessed.

Winds, waters, country, seasons and non-compliance with specified regimens have been considered to be responsible for fevers and infections by Charaka, Hippocrates and other ancient physicians like Chang Chung Ching (A.D. 150 – 200). Whether, besides the bacterial proliferation and spread, host immune surveillance could be influenced by extremes of weather etc. could be an important question. Immunology is a very rapidly advancing field of research. There are remarkable developments taking place in the fields of monoclonal antibodies and the mechanism control of T and B cell functions; the precise roles of macrophages, eosinophils and mast cells are also being actively pursued. An interface of Ayurvedic therapy and modern immunology may provide a novel field for research. Several therapeutic modalities in

Ayurveda are claimed to be useful in recurrent infections or autoimmune diseases. The sophisticated techniques and models of the modern immunology can be gainfully employed for such research. Immunology of malignancy is a field that is currently begging for new paradigms. The tumour marker antigens and the derepression of foetal antigens hint at the attempts to activate a defective immune surveillance. Are the host factors more important in rapid spread of the metastases than the anaplastic nature of the tumour? Why does a neuroblastoma regress back to ganglioneuroma? AIMD plans to embark on a careful study of patients with incurable cancer who opt for and claim benefit from unconventional forms by therapy with natural products and plants.

'Wisdom of the body' is one of the finest chapters in this monograph. The interaction with late Acharya Vinoba Bhave also provides interesting humour. The traditional Hindu aversion to 'allopathic poisons' is an anti-scientific attitude deeply ingrained in our culture. The body-mind dichotomy is artificial and wisdom of both body and mind is essential for health and happiness. 'Pragnaparadh' is a unique concept of Ayurveda that needs to be investigated scientifically. That suppression of natural urges can lead to diseases, is a unique Ayurvedic concept. Prof. Marson's studies in England have shown that diverticulosis may be initiated by pouches produced by the back pressure by habitual suppression of defaecation urge.

The universe of traditional remedies and herbs is a mixed bag. The gems may be hidden in a mass of placebos or mildly active plants. It is essential to concentrate herbal research on the priority areas of maximal national and international concern. It is redundant to concentrate in fields where very potent and rational modern drugs are already available and have shown dramatic therapeutic modalities for diseases, for which only symptomatic remedies are available would be more cost-effective. Our approach has been to concentrate on scientific clinical validation of safety and efficacy first and then develop phytochemistry, pharmacology and toxicology. The major areas of interest would be – arthritis, jaundice (viral hepatitis), cancer, diabetes, atherosclerosis, allergic skin disorders, peptic ulcer, irritable colon and disorders of aging. Only a multidisciplinary, dedicated effort can be productive, as shown by work on Arogyawardhani, Mucuna pruriens etc. Modern methods in pharmacodynamics, pharmacokinetics and drug metabolism provide good information on what the drug does to the body and what the body does to the drug. The information helps in rational therapy with maximum benefit and minimal hazards. Such a systematic exploration of the commonly used Ayurvedic formula-

tions and drugs is essential. Sometimes we do not have any idea of the maximally tolerated human or animal doses of common Ayurvedic drugs. We recently studied, in healthy volunteers, the tolerability of *Yogarajguggulu.* Side effects were observed with high doses. Animal studies with complex formulations and plants are not easy to perform and offer new challenges in quantitative administration. Toxicology of heavy metal formulations of Ayurveda must be studied critically in animals and patients. The claim that Ayurvedic drugs are all non-toxic is a partisan belief not based on data. If we intend to use Ayurvedic drugs scientifically, their toxic profile should be known. Clinical toxicology is not much developed in India. Agadtantra in Ayurveda was an important subject because of the attempts at poisoning kings and other VIPs. A poison centre with fully equipped analytical and resuscitative facilities is non-existent in India. We have occasionally assisted in monitoring drug levels in patients with attempted suicide. The modern analytical methods like H.P.L.C., G.L.C., GC/MS, etc. can offer life saving data on poison-levels in blood, urine etc. In our nation, hygiene is very poor. Prof. Lele has shown in the chapter on "hygiene and public health" that much of our suffering stems from our poor habits of hygiene and inadequate measures of public health. The principles of hygiene were not only well stated in Ayurvedic books but also in *puranas* and books on ethics:

Upaanahau cha vasascha dhrtamanyairna dharayet
Upavithamalankaram srajam karakameva cha. *(Manu)*

"One should not use the footwear, clothes, sacred-thread, ornaments, garland worn by others and the drinking utensils used by others".

It is desirable to inculcate the sense of hygiene in all people. "Gandagi Hatao" can indeed be a movement, like the 'patriotic health movement' in China. In China, using boiled water and carrying one's water supply gradually became a norm among the students and young people. In the past, much of our hygiene was tied up with our religious practices and rituals. With the general debunking of superstitions, certain good hygienic habits have also been abandoned.

'Periodic health check-ups' is an excellent chapter of the monograph written by an astute physician who has a very large experience in this field. Often the psychological defences work against the submission for a health check-up. One may worry about the diagnosis of an incurable disease. The attitudes of those who cheerfully subject themselves to a regular check-up vs. those who do not like it will have to be studied by in-depth interviews and personality-rating scales. All schools and colleges should have their regular periodic health check-up schemes.

Health awareness should be every student's topmost concern. Such a project should also include a survey of the habits of students as to exercise, food, alcohol, Yoga, etc. Students must be made partners in the project. Special prizes can be awarded for health-awareness and sickness-free years. AIMD has taken up one such project at the Andheri campus of Bhavan's colleges. The data generated may serve as models for the programmes for student health care.

The aged and mother/child also need special attention in health check-up programmes. At a very nominal charge, complete check-up should be available to our elderly citizens. And even advice for the diseases of the aged can be given. Mother and child health programmes can be developed in an integrated manner. *Kashyapa Samhita* has been a relatively neglected treatise that has a wealth of information on the subject.

Lastly, this tremendous effort by Prof. R. D. Lele to build a bridge would be adequately rewarded if inspired by it some of our young biomedical students embark on undergraduate, post-graduate doctoral and post-doctoral projects in diverse aspects of linking Ayurveda and Modern Biomedicine.

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Vice Chairman
Life and Health Sciences Division
Bhavan's Ancient Insights and Modern Discoveries Project

PROLOGUE

The Bharatiya Vidya Bhavan launched in 1977 a project entitled "Ancient Insights and Modern Discoveries", which is a national cooperative endeavour to explore the possibilites of meaningful correlations of ancient ideas and concepts and modern scientific discoveries. For the last several years I have been studying with great interest and an open-minded curiosity, the ancient Ayurvedic classics, *Charaka Samhita* and *Sushruta Samhita.* My approach to the study of Ayurveda through the eyes of a 20th Century physician trained in and practising "Modern", "Western", "Cosmopolitan" medicine, is illustrated in the following letter which I wrote to the Editor of "Science" (U.S.A.) and which appeared in its October 8, 1982 issue on page 110:

"T. L. Lentz et al (Reports, 8 Jan, 1982, P. 182) provide evidence to suggest that acetylcholine receptors may serve as receptors for rabies virus. In *Sushruta Samhita,* the ancient Indian Classic on the Science of Life, there is a fascinating account of *Datura* as a prophylaxis for rabies. Datura is to be given by mouth immediately after a dog bite, in a dosage sufficient to produce dilatation of the pupils and symptoms of mild delirium which pass in a day or two, when the next oral dose is given to produce similar symptoms. Several such doses are recommended. The treatment is to be started as early as possible because, once the clinical symptoms of rabies become manifest, the disease is fatal (*Kalpa Sthanam,* Chapter 7, Stanzas 49 – 59).

The active principles of Datura Strammonium, like Atropa Belladona, are atropine and related alkaloids that predominantly block the muscarine action of acetylcholine. In view of Lentz's findings, Datura for rabies may represent the first documented example of prophylaxis by receptor blockade.

Because clinical rabies is fatal and anti-rabic vaccine is routinely administered to victims of bites from rabic dogs, it is not possible to conduct a controlled clinical trial to assess the efficacy of Datura prophylaxis. However, it would be interesting to compare the effectiveness of antirabic vaccine with acetylcholine inhibitors such as atropine, in experimental animals."

I do not wish to hide my preference for modern scientific medicine, yet I have noted with admiration the vast conceptual framework and canvas of Ayurveda, being very similar to the 20th Century concept of Life Sciences. Ayurveda (Science of Life) is not confined to Medicine but encompasses the total sweep of life sciences and pursues the quest for understanding life in all its ramifications. Life is the most fascinating phenomenon within the ken of man and the 20th Century has revealed some of the greatest insights into our understanding of life at increasingly higher levels of organization — molecular, subcellular, organelles, cells, tissues, organs, organisms, species and ecosystems — and to me the most remarkable feature of modern medicine is its close integration with the basic sciences-physics, chemistry and biology. Throughout this book I have illustrated the evolution of current medical knowledge from the intuitive, observational and empirical ancient beginnings to the modern era of experimental medicine. Acceptance of this knowledge and its assimilation into the thinking process is what Charaka and Sushruta themselves would have expected from their 20th Century descendants, as is clearly evident from the following passage:

"The Science of life shall never attain finality. Therefore humility and relentless industry should characterize your every endeavour and your approach to knowledge. The entire world consists of teachers for the wise and enemies for the fools. Therefore, knowledge, conducive to health, longevity, fame and excellence, coming even from an unfamiliar source, should be received, assimilated and utilised with earnestness".

(*Charaka Samhita,* Vimana Sthana, 8, 14.)

However much the knowledge base of the physician has changed the fundamental commitment of the physician to the care of the patient remains unaltered. One criticism of modern scientific medicine is that it encourages a disease-oriented, rather than patient-oriented approach, thinking in terms of a "case" rather than a "person". Critics who talk of the dehumanising effects of modern medical technologies would do well to note the following opening passage which has been appearing for over 33 years in the most popular and prestigious modern text book of Medicine (Harrison's *Principles of Internal Medicine):*

"Tact, sympathy and understanding are expected of the physician, for the patient is no mere collection of symptoms, signs, disordered functions, damaged organs and disturbed emotions. He is human, fearful and hopeful, seeking relief, help and reassurance. To the physician as to the anthropologist, nothing human is strange or repulsive. The

misanthrope may become a smart diagnostician of organic disease, but he can scarcely hope to succeed as a physician. The true physician has a Shakespearian breadth of interest in the wise and the foolish, the proud and the humble, the stoic hero and the whining rogue. He cares for people.''

This is truly the Ayurvedic approach. Scientific approach and humanism in medicine are not mutually exclusive.

In my study of Ayurveda I have found a lot to be admired, and also a lot to be rejected. What I have admired and found acceptable and relevant even for today's thinking is described in the first chapter.

I have preferred not to enumerate the things which in my opinion are worthy of rejection. Instead, I have emphasised the method of science and the spirit of science. Curiosity to examine with an open mind any idea or any proposition, and scepticism in its acceptance unless valid supporting evidence is provided, make an ideal blend in a Scientific mind. That way one is safeguarded against missed opportunities and false hopes. Uncritical acceptance and uncritical rejection of any idea or proposition are both equally inimical to the spirit of Science and to Scientific advancement. Due to the impact of *Clinical Science* in the last fifty years, modern medicine has made a severely critical self-appraisal and found that a lot of prevalent therapy was useless. I can only hope that teachers, students, and practitioners of Ayurveda and Homoeopathy will apply the same searching scrutiny to their own concepts and practices, as modern medicine has done in the last five decades. This is in fact, a legitimate function and duty of teaching institutions and Faculties affiliated to Universities, throughout the country.

My approach to the study of Ayurveda has been guided by the following two quotations. The first one is by Thomas Henry Huxley in 1881:

''It is easy to sneer at our ancestors — but it is much more profitable to try to discover why they, who were really not one whit less sensible persons than our own excellent selves, should have been led to entertain views which strike us as absurd''.

The other quotation is from Oliver Wendell Holmes about Emerson:

''Here was an iconoclast without a hammer, who took down his idols from their pedestals so tenderly that it seemed like an act of worship''.

— *Dr. R. D. Lele*

CONTENTS

Chapter I

AYURVEDA THROUGH MODERN EYES

Introduction

Historians of Modern Cosmopolitan Medicine consider Hippocrates (460-370 BC) as the founder of medicine as we know it today. Hippocrates gave medicine its scientific spirit, replaced superstition by rational observation and inference, gave a rational diagnosis, prognosis and treatment, and gave medicine its ethical ideas. The Hippocratic oath is taken even today and the Hippocratic aphorisms are admired as gems of human clinical wisdom even by the student of medicine in the 20th Century. Take for instance, the following aphorism: "In case of jaundice, hardening of the liver is a bad sign".

Without detracting a bit from the tributes rightly paid by medical historians to Hippocrates, it can be affirmed that Charaka and Sushruta deserve the same primacy and the same place of honour as Hippocrates. Indian historians claim that Charaka and Sushruta came before the time of Hippocrates, while some western historians put the time of Sushruta much later (1st Century A.D.). The controversy and dispute about the determination of the exact time of Charaka and Sushruta are irrelevant to the proposition that Charaka & Sushruta deserve the same pre-eminence as Hippocrates, as founders of Medicine. Despite the great contributions made by the western Indologists in the last 100 years, in establishing the greatness of ancient Indian Medicine, ignorance and/or prejudice of western medical historians continue even today as evidenced by the fact that a most recent (1978) *Life Magazine* publication on the history of Médicine does not even mention Charaka and Sushruta.

The History and Literature of Ayurveda

The term Ayurveda means "Knowledge"*(Veda)* concerning maintenance of "life" *(ayus)*. The origins of this knowledge are already

evident in the Atharvaveda (the contents of which can be dated between circa 1500-1000 BC). The treatment of disease *(Chikitsa)* in the Atharvaveda is largely religious and ritualistic, emphasizing such practices as the "sacred utterances" *(mantra)*, penances *(niyama)*, amulets *(mani)*, sacred oblations *(mangala homa)*, fasting *(upavasa)*, and purificatory rites *(prayaschitta)*, but the Atharvaveda also contains material about human anatomy, herbal medicines *(bhaisajya)*, and the classification of diseases *(lingi vyadhi)*. Reference is made to "wandering medical practitioners" *(charan-vidya)* and those who are "trained in medical science" *(Vaidya)*. Mythologically the first exponent of the medical science was none other than the creator *Brahma* himself. *Brahma* shared this knowledge with Prajapati, who in turn passed on the tradition to the Ashwini Kumaras and Indra. Surgery *(Shalya)* was revealed by Indra to Divodasa, the King of Kasi who was also an incarnation of the divine *Dhanvantari*, culminating finally in the classical *Sushruta* tradition of Ayurvedic surgery and medicine. Internal medicine *(Kaya-Chikitsa)* was revealed by Indra primarily to Atreya Punarvasu, culminating finally in the classical *Charaka* tradition of Ayurvedic general medicine. Ayurveda is considered as a supplement *(upanga)* or as an *upaveda* (supplementary veda) of Atharvaveda, or even as a "fifth veda" (the four vedas being Rig, Sama, Yajur and Atharva).

Numerous other texts of medicine, other than *Charaka Samhita* and *Sushruta Samhita* were regularly composed through the centuries, such as the *Bhela Samhita, Kashyap Samhita,* and *Agnivesha tantra* (which were even earlier than Charaka Samhita). Other notable contributions were *Ashtanga Hrdaya* of Vagbhata (600 AD) and *Madhav Nidana* (700 AD). The Ayurvedic tradition continued as a vigorous and expanding scientific tradition down into the 16th Century. Its medical literature is oriented practically and operationally, although apparently it had an "elective affinity" for and an ongoing exchange with the classical Indian philosophies. The dominant intellectual influences on Ayurveda are those of the *Samkhya* and *Vaisheshika* Indian philosophies, although one also finds terms and notions from the *Vedanta. Nyaya, Yoga* and early Buddhist and Jain reflections.

For the modern reader, the texts present a symposium-like format in which a practical problem like fever*(Jvara)* or dysentery *(atisara)* or a disease such as pulmonary tuberculosis *(rajayakshma)* is discussed, classified as to type, contextualised (with respect to prodrome, syndrome, prognosis) and finally dealt with therapeutically.

Ayurvedic texts were translated into Greek by Cnidos (300 BC), Tibetan and Chinese (300 AD), Persian (700 AD) and Arabic (800 AD).

The Scope & Contents of Charaka Samhita

Charaka Samhita (literally, treatise compiled by Charaka) is a Sanskrit work of great antiquity. It is an exposition of Ayurveda, the science of life, defined as the Science of the causes and symptoms of disease, of their treatment and of the maintenance of health *(Sutra 1, 23)*. It also deals with the origin of medical science, the fundamental causes of conception and birth and of physical deformities. The treatise contains a detailed classification and nomenclature of diseases—their *Vyakhya* (definition), *Vyutpatti* (etymology), *Nidana* (etiology), *Poorva Roop* (prodromata) and *Roop* (clinical picture), *Samprapti* (pathophysiology), *Sadhya Sadhatva* (prognosis), *Chikitsa Sutra* (line of treatment), *Aushadha* (drugs), *Anna* (diet) and *Vihara* (practices), etc. This conceptual framework and approach appear strikingly similar to contemporary medicine.

According to Charaka, Ayurveda has eight branches (*Sutra 30.* 30)

1. *Kayachikitsa* (internal medicine & therapeutics)
2. *Shalakya,* the science of special organ diseases—eye, ear, nose, throat etc.
3. *Shalyapahartrka,* Surgery
4. *Visha garavairodhikaprasamana,* toxicology
5. *Bhuta vidya,* psychiatric knowledge
6. *Kaumarabhrtya* paediatrics
7. *Rasayana,* rejuvenation
8. *Vajikaran,* virilification.

For the discussion of the above topics the treatise is divided into eight sections. (Sutra *30.* 35)

1. *Sutra Sthana* deals with general principles, philosophy etc.
2. *Nidana Sthana* deals with causes of diseases
3. *Vimana Sthana* deals with taste, nourishment and general pathology etc.
4. *Sharira Sthana* deals with anatomy and embryology
5. *Indriya Sthana* deals with diagnosis and prognosis
6. *Chikitsa Sthana* deals with treatment of diseases
7. *Kalpa Sthana* deals with pharmacy
8. *Siddhi Sthana* deals with the cure of disease.

In all there are 150 chapters on specific topics. There are at places some later revisions and interpolations, as repeatedly admitted by the redactor at the end of each and every chapter. In fact, Dradhbala states that he had to rewrite and complete the last section *Siddhi Sthana* from the material available to him (*Sutra 12.* 55).

Scope and Contents of Sushruta Samhita

The approach of *Sushruta Samhita* is similar to *Charaka Samhita,* but with special emphasis on surgery, which Sushruta describes as the first and foremost speciality. He has described various types of inflammation and various stages of inflammation, accidental wounds, burns, fractures. Sushruta describes many major abdominal operations for intestinal obstruction, bladder stones etc. and also plastic surgery like rhinoplasty, crushing and extracting the foetus, delivering the foetus through abdominal operation, amputation of limbs and extraction of foreign bodies. Sushruta described *"Shalya"* or surgery as the highest in value among the therapies because of its ability of producing instantaneous relief by means of instruments and appliances.

Sushruta has described 101 kinds of blunt instruments and 21 kinds of sharp instruments. The 101 blunt instruments are sub-divided into:

Swastika or Cruciform, 24 kinds
Samdamsa or pincer-like, 2 "
Tala or picklock-like 2 "
Nadi or tubular, 20 "
Shataka or pricker-like, 28 "
Upayantras or accessories, 25 "

The very first of these, *Simhamukha Swastika* (lion-faced forceps) is the precursor of the modern lion's forceps.

The blunt instruments cover a wide range including forceps, pincers, trocars, speculums (nasal, aural, vaginal), finger guards, syringes, cannulae, dilators, catheters, clysters with eight kinds of bags and tubes, catheters, tubular appliances for inhalation, fumigation and disinfection of rooms, rods, probes of different shapes and sizes, foetus traction hooks, bone levers, directors and many others.

The accessories include thread (also caustic coated thread—*"Kshara sutra"* for the operation of fistula-in-ano), twine for ligature, bandages of 14 types, dressings, abdominal binders, various types of leather bags, bands and bandages, splints (made of bamboo and inner bark of trees),

crutches, tendrils and creepers, cloth, spittle, suture material, caustic medicines and goat's guts.

The sharp instruments include knives and scalpels (many varieties), saws, ring scalpels, needles, scissors, *trikurcha* (triple-needle trocar), axes, awls, tooth-scalers and sharp hooks.

Sushruta emphasises that "the hand of the surgeon is the best, the most useful and the most important of all surgical instruments".

Thirtytwo surgical manoeuvres are described by Sushruta. Some examples: *Nirghatana* (extraction by moving to and fro); *Vyuhana* (raising up and incising a part bringing together the lips of the wound); *Vartana* (contracting or curling up); *Chalana* (moving a foreign body); *Vivartana* (turning round); *Peedana* (pressing out); *Vikarsana* (loosening); *Aharna* (pulling up); *Unnamana* (elevating depressed cranial bones); *Darana* (splitting); *Chhedana* (excision); *Bhedana* (incision); *Unmathana* (probing); *Achusana* (suction); *Lekhana* (dissection); *Vyadhana* (puncturing); *Visravana* (draining) and *Sivana* (suturing).

Ayurveda as a Life Science

One is impressed by the vast conceptual canvas and framework of Ayurveda. It is important to realise that Ayurveda is not confined to Medicine only, it tackles the whole subject of life in its various ramifications. This can be seen by the variety of topics discussed therein, such as re-birth, renunciation, salvation *(Moksha)*, soul *(Atma)* etc.

The *purpose of life* is four-fold, to achieve *dharma* (virtue), *artha* (wealth), *kama* (enjoyment) and *moksha* (salvation). In order to attain success in this four-fold purpose of life, it is essential to maintain life not only in a disease-free state but also in a positively healthy state of body, mind and spirit.

The emphasis on the *maintenance of positive health* or *Swastha Vrutta*, is a distinguishing feature of Ayurveda. In order to maintain positive health, Ayurveda prescribes specific daily routine *"dinacharya"*, and also a seasonal regime *"ritucharya"*. In *"dinacharya"* great importance is given to *diet* which is to be taken in a proper way with regard to quality, quantity as well as frequency. Emphasis is given to physical exercise and personal hygiene. The daily regime advocates not to suppress certain natural physical urges like micturition, defecation, hunger, thirst, sleep etc. On the other hand suppression of harmful psychic urges is

advocated—like greed, fear, anger, vanity, jealousy, malice and excessive attachment to anything.

Equal importance is given to *mental health,* for which a regime of *Sadvrutta* (ethical life) is prescibed. Strict mental discipline and strict adherence to moral values is considered a pre-requisite for mental health.

"That is named the Science of Life wherein is laid down the *good* and *bad* life, the *happy* and the *unhappy* life, and what is *wholesome* and what is *unwholesome* in relation to life, and also the *measure* of life." *(Charaka Samhita,* Sutra Sthana, *1,* 41).

An interesting concept worth emphasizing here is that of *Vyadhi-Kshamatwa,* that is resistance to disease (or immunity in modern parlance). The aim of Ayurveda is to promote health—*"Swasthasya Swasthya rakshanam",* increase immunity and resistance—*"Vyadhi Kshamatva"* and to cure disease—*"Aturasya Vyadhi parimokshah".*

In spite of the fact that Ayurveda has laid great stress on *"Bhuyo Darshana"* (repeated observation) and acceptance of data as reliable only on the basis of *"Anvaya"* (uniform consistency), unmarred by any *"Vyatireka"* (contradiction), *intuition* has played a major role in the development of Ayurvedic concepts. But it is remarkable, from a clinician's viewpoint that the clinical approach of the Ayurvedic physician seems strikingly similar to that of the modern physician, as will be seen from the next section.

The Clinical Approach in Ayurveda

According to Charaka, there are three means open to the physician for ascertaining the nature of any sickness; they are: (i) theoretical knowledge of the possible causes and symptoms of all known diseases; (ii) meticulous observation of the patients' symptoms and signs and complaints; (iii) inference based on previous experience. In the absence of one or more of the three aids to diagnosis, or with their fragmentary or incorrect knowledge, the physician cannot come to a true conclusion (Vimana, *4,* 3-5).

If one reads Sushruta's description of the clinical methods it appears very contemporary.

"The physician should interrogate *("prashna")* the patient about his complaints in great detail. He should use the five senses of sight, touch, hearing, smell & taste, in addition to oral enquiry".

"Fullness or emaciation of the body, state and indications of vitality, strength, complexion etc. are perceived by the sense of *sight*".

"The heat and coldness of the body, gloss, roughness, hardness or softness of the skin of the affected part as in fever or in an edematous swelling of the body, are perceptible by the sense of *touch*".

"The *vayu* making the blood ebullient, forces it up with a distinctly audible report and thus affects the sense of *hearing*. Diseases which can be diagnosed with the help of hearing will be fully dealt with in the chapter on *Vrana Srava*".

"The characteristic smell emitted by an ulcer in its critical stage (*"Arishta"*) should be determined with the help of the organ of *smell*".

"Secretions or discharges should be tested with the organ of *taste*. In *"prameha"* & *"Madhumeha"* (diabetes) one should watch the urine being or not being swarmed with hosts of ants or flies".

"Such facts as the *time* or *season* of the first appearance of the disease, the *caste* to which the patient belongs, and things or measures which tend to bring about a manifest amelioration of the disease or prove comfortable to the patient (*"Satmya"*), similarly the factors which cause aggravation of the pain, the strength of the patient, his appetite and state of digestion, the emission of stools, urine and flatus or their stoppage, the maturity of the disease as regards time, should be specifically ascertained by directly interrogating the patient on those subjects".

"A disease wrongly observed or incorrectly described is sure to mislead the physician".

The *observational* or *empirical approach*, the classified entity being a phenomenon that has actually been witnessed, formed the basis on which the Ayurvedic physician made *inferences* based on the *"Tridosha"* theory.

Every disease, whether acute or chronic, mild or severe, passes through certain stages. These stages are called *kriyakala* or the time for treatment. They are six in number: (1) *Sanchaya* or accumulation of morbid *dosha* (2) *Prakopa* or vitiation of dosha (3) *Prasara* or spread of dosha (4) *Sthana-sanshraya* or localization of dosha (5) *Vyakti* or manifestation of disease and (6) *Bheda* or chronicity, complications etc.

In the clinical assessment in Ayurveda, there are two words used—*Rogi pariksha* (examination of patient) and *Roga pariksha* (examination of disease).

Rogi pariksha (examination of the patient) is carried out to assess his life span, *"Ayushah-pramana"*; strength, *"bala"*; and intensity of morbidity, *"Dosha pramana."*

In assessing the strength and morbidity of the patient. the following ten points are to be examined:
(1) Constitution of the patient or *"Prakriti"* (2) pathological condition or *"Vikruti"* (3) perfectness of body tissues or *"Sara"* (4) Compactness or *"Sanhanana"* (5) proportions of the limbs or *"pramana"* (6) homologation or suitability—*"Satmya"* (7) psychology or *"Satwa"* (8) Capacity for food and its digestion, *"Ahara Shakti"* (9) Capacity for work and exercise, *"Vyayama Shakti"*, and (10) age of the patient, *"Vaya"*.

Based on all these ten factors, the strength of the patient can be assessed as either high—*"Pravara"*, medium—*"Madhya"* or low—*"Avara"*.

The concept of therapeutic test or *Upashaya* is worthy of note. There are certain diseases where the diagnosis becomes difficult or impossible. In such cases, Charaka recommends *Upashaya,* or the use of medicines, diet and regimen which are antagonistic directly or in effect to the causative factor, disease or to both.

Other points to be taken into account are the exciting factors or *"Prakopana Nidana"*, onset or *"Utthanam"*, location or *"adhisthana"*, stage of aggravation or *"Vriddhi"*, abatement or *"Kshaya"*, sequelae or *"Udreka"*.

The assessment of the results of treatment or *"Karya phalam"* is to be based according to Charaka on four criteria or *"Chabis-shreyas"*.

The indications of cure from a disease are described as:

(1) *"Rug-upashamanam"* or relief from pain & disease.
(2) *"Swara-varna yoga"* or accession of voice and complexion.
(3) *"sharira upachaya"* or increase in body weight.
(4) *"Bala Vriddhi"* or regaining strength and vitality.
(5) *Abhyavaharya Abhilasha* or desire for food.
(6) *Ruchini Ahara kala* or relish while eating.
(7) *Samyak Jaraman* or timely and proper digestion of food.
(8) *Nidra labha yathakalam* or sleep at proper time.
(9) *Vaikarikanam Swapnanam adarshanam* or not seeing frightful dreams.
(10) *"Sukhena pratibadhanam"* or happy awakening.
(11) *"Vata-mutra purisha retasam Mukti"* or normal elimination of flatus, stool, urine and semen.
(12) *Sarvakaraihi Mano Buddhi indriyanam Avyagatti* or freedom from impairment of any kind of the mind, intellect and sense organs.

The scope of Ayurvedic treatment consists of a salubrious use of (a) *"aushadha"* (drugs), (b) *"Anna"* (diets) and (c) *"Vihara"* (practices), prescribed jointly and severally:

(i) contrary to the cause of disease, or
(ii) contrary to the disease itself, or
(iii) contrary to both the cause and disease, or
(iv) similar to the cause of disease, or
(v) similar to the disease, or
(vi) similar to both the cause and disease.

"Shodhana" and "Shamana" concepts.

"Shodhana" means purification of the body through *vamana* (emesis), *virechana* (purgation), *Basti* (enema), *Shirovirechana* (nasal medication) and *rakta mokshana* (blood letting). It is also called *"Pancha Karma"* or five-fold line of treatment. *"Shamana"* means subsidence of disease and symptoms by *Kshut* or *langhana* (fasting or light diet), *Trit Nigraha* (restriction of fluids), *Vyayama* (exercises), *"atapsevan"* (sun rays), *maruta sevan* (breeze of air).

Certain other methods of treatment or *Upakramas* are: *"Brimhana"* or Methods to increase body weight (as against methods to reduce body weight by *"langhana")*. *Snehana* or administration of oily or fatty substances by food and drinks, enemata or through the skin by oily massage (as against *Rukshana* or reduction of fat). *Stambhana* or procedures by which the flow of fluids in the body is lessened or checked (as against *Swedana* or procedure to induce sweating, by applying dry heat, steam, poultices or hot liquids).

Another interesting concept is *Srota-Suddhikara Chikitsa* or to get normal flow of the flowing materials in the body.

Rasayana chikitsa is aimed at controlling the ageing process and increasing strength and vitality.

Vajikarna is aimed at increasing pleasure in the sex act and procuring healthy progeny.

Optimal timing of drug administration in relation to meals

Ayurveda describes the following ten timings of giving of drugs in relation to meals:

1. *"Abhukta"* – on empty stomach
2. *"Pragbhukta"* – pre-prandial
3. *"Adhobhukta"* – post prandial

4. *"Antarabhukta"*	– in between meals
5. *"Madhyebhukta"*	– in the middle of the meal
6. *"Sabhukta"*	– mixed with the meal
7. *"Sa mugda"*	– given in the beginning and at the end of the meal
8. *"Muhurmuhu"*	– Repeatedly
9. *"Grasa"*	– with every morsel of food
10. *"Grasanter"*	– In between morsels.

It is interesting that we use similar considerations today with the aim of improving absorption and minimising gastric irritation:

1. Drugs taken 1 hour before or 2 hours after a meal for more rapid absorption
   Oral antibiotics
   penicillamine
2. Drugs taken half an hour before meals
   anti-cholenergics—to decrease gastrointestinal motility
   Appetite depressants – to reduce food intake
   Dopamine antagonist (metoclopramide) – to prevent nausea
3. Drugs taken with meals to prevent gastric irritation or improve absorption of lipid-soluble drugs

Cimetidine	oral hypoglycemic agents	Hydralazine
Corticosteroid	potassium, iron supplements	Hydrochlorothiazide
Theophylline	Anti-TB drugs	Propoxyphene
Anti-inflammatory drugs	Urinary antiseptics	Griseofulvin
Aspirin	Propranolol Diphenyl hydantoin	Spironolactone Carbamazopine

4. Drugs taken half hour after meals to relieve gastric upset:antacids.

Relevance of Ayurveda Today

Eminent modern medical men in India have written extensively about our glorious ancient medical heritage (Kutumbiah, Bhatia, R. J. Vakil,

Keswani etc.). The Government Medical College & Hospital at Aurangabad in Maharashtra, with which the author was associated, is an institution of Modern Medicine; the staff and students of this Institution unanimously named the College & Hospital campus after Charaka, Sushruta and Dhanvantari.

As a student of Modern Medicine, having studied both Hippocrates and Charaka & Sushruta, I find remarkable similarity of approach between the Greek and Indian Masters. It is quite likely that these great masters were contemporaries and were influenced by the ideas of each other, as happens in contemporary cosmopolitan medicine. One major difference is that in Hippocratic literature there are 42 clinical cases, almost the only records of the kind for the next 1700 years. In *Charaka Samhita* and *Sushruta Samhita* we do not find such individual clinical case records. What we find are declarative statements which represent the crystallisation of an accumulated experience derived from observation of natural phenomenon and the application of logic, both inductive and deductive, to make generalisations, which have a universal appeal.

For the benefit of those who have not had the opportunity of studying the original texts, I have compiled selected passages and Ayurvedic Aphorisms which to my mind have relevance even today.

Ayurveda as a Life Science

"Health is the supreme foundation of virtue, wealth, enjoyment and salvation. Diseases are the destroyers of health, of the good in life, and even of life itself. Thus has arisen the great impediment to the progress of humanity".

"That is named the Science of Life wherein are laid down the good and the bad of life, the happy and unhappy life, and what is wholesome and what is unwholesome in relation to life, as also the measure of life".

"The Science relating to life is regarded by the philosophers as the most meritorious of all the sciences because it teaches mankind what constitutes their good in both the worlds".

"Life is spoken of as the union of the body, senses, mind and spirit. The body, mind and spirit together are, as it were, the tripod".

"The body and the mind are both considered to be the abodes of disease, likewise, of well-being. The cause of well-being is their harmonious and concordant interaction. The cause of disease, psychic or somatic, is either erroneous, absent or excessive interaction".

"The objective of the Science of Life is establishing equilibrium of the body elements".

"The morbidity of the body is remedied by medication; the morbidity of the mind by spiritual knowledge, philosophy, fortitude, remembrance and concentration".

The Nature of Happy Life

"Life of such a man is called happy as is not afflicted with either bodily or mental ailments, as is endowed with youth, strength, virility, reputation, enterprise and boldness befitting his abilities, is actuated in his deeds by the combined urge of knowledge, science, the senses and the sense objects, is possessed of multifarious and delightful amenities occurring from great wealth, whose efforts are prosperous and who can plan as he likes. A life to the contrary is deemed unhappy".

The Nature of Good Life

"The life of that man is said to be good who is a well-wisher of all creatures, who does not covet other people's goods, who is a teller of truth, who is peace-loving, who acts with deliberation, is not negligent, is devoted to the three ends of life viz., virtue, wealth and enjoyment, without letting any one to come into conflict with the other two, who is reverential to those who are worthy of reverence, who is of a scholarly, scientific and retiring disposition, partial to the company of elders, who can curb his passions of desire, anger, envy, pride and conceit, who is constantly given to charitable acts, and contemplative of the good in this world and the next, and endowed with memory and understanding."

Life of the opposite nature is said to be "not good".

Code of Conduct for Healthy Living

"The wise man who seeks happiness both here and hereafter, should exercise the highest care in selecting what is wholesome in the matter of food, conduct and behaviour."

"The length of life is a matter of care and husbandry. The opposite condition leads to death. He who rightly observes the rules of health as laid down here will not be deprived of the full measure of hundred years of diseaseless life."

Virtues of Clean Habits

"Virtues of cleaning the teeth, scraping the tongue and cleansing the

mouth, massage and bathing, wearing of clean apparel, trimming of hair, beard and nails, frequent ablution of the feet and the excretory orifices, have all been emphasised. Like the lord of a city in the affairs of his city, a charioteer in the management of his chariot, so should a wise man be ever vigilant in the care of his own body."

"By degrees, the wise man should free himself from unwholesome habits; also by degrees he should develop wholesome habits. By gradual withdrawal, addictions do not revert; and wholesome habits, gradually acquired, become firmly implanted".

Virtues of Measured Diet

"Food is the principal factor which materially contributes to the strength, complexion, vitality of animated beings".

"That should be known as the proper measure of food which when taken, is digested in due time without impairing one's health".

"An excess or surfeit of food is markedly harmful unless the gastric fire is increased by hard exercise."

Importance of Exercise

"That activity of the body. which is meant to increase its strength and firmness is regarded as physical exercise. It should be practised regularly in the right measure. Lightness, capacity for work, firmness, tolerance to hardship, subsidence of humoral discordance and stimulation of gastric fire accrue from exercise."

"Fatigue, exhaustion, wasting, thirst, asthma, cough, fever and vomiting result from over-exercise."

Ethical Conduct

"Mind control consists of restraining the mind from the desire for unwholesome objects".

"A wise man should not suppress the natural urges of urine, faeces, semen, sneezing, yawning, hunger, thirst, sleep, tears, and deep breathing after exertion."

"On the other hand, those desirous of their welfare both in this and the next world, should suppress the rash and evil impulses of the mind, speech and body. The wise man should control the impulses of greed, grief, fear, anger, vanity, impudence, jealousy, excessive attachment, and malice. One should control the impulse of speech that is harsh, extravagant, insinuating, untrue and untimely. One should control the

impulse for all such activities as are injurious to others such as adultery, theft and violence."

"One should have recourse to such means of livelihood as are not contrary to the dictates of religion. One should be devoted to peace and scholarship. Living thus, one attains happiness."

"Do not give way to anger and joy, do not nurse your sorrows, be not arrogant in success and dejected in defeat, remind yourself constantly of the vanity of things, be decided as to causes and their effects and consequently devote to benevolent enterprises; do not grow complacent with your achievements; do not lose heart; do not recall calumny."

"Diseases occur in those who do not observe the rules of healthy living. Hence the healthy man should be diligent in the observance of the rules of healthy living".

"He alone can remain healthy, who regulates his diet, exercise and recreation, controls his sensual pleasures, who is generous, just, truthful and forgiving, and who gets along well with his relatives."

Homeostasis, the Aim of Therapy

"Medicine is that, which being well administered, becomes an equaliser of increased and diminished elements at the same time. It brings down the excessive element and augments the deficient one."

"Indeed this alone is the end sought in the employment of medicine, as also in the observance of wholesome habits, that the equilibrium of the elements may be achieved or maintained as the case may be. For it is only with a view to help maintain the balance of the elements that the intelligent will make use of a balanced diet. By the use of like and unlike food and exertion, the increase and diminution of body elements are brought about opportunely to restore equilibrium."

"There is in the World no substance that may not be used as medicine, in this or that manner, for this or that purpose."

"Medicine is of two kinds—one kind is promotive of vigour in the healthy. The other is destructive of disease in the ailing."

"The opposite of medicine is also of two kinds—the one causing immediate disorders and the other causing remote ill-effects".

"That which is of contrary character to medicine is to be known as 'contra-medicine'. It is unfit for use. We shall confine to describing that which alone is fit for use".

The Four Pillars of Treatment

"The physician, the drugs, the attendant and the patient constitute the four basic factors of treatment. Of these four, the physician occupies the chief place, being at once the knower of disease and drugs, the instructor of the attendant and patient, and prescriber of medicine and regimen."

The Qualifications of a Physician

"Clear grasp of theoretical knowledge, wide practical experience and skills, purity of body and mind, these are the tetrad of desiderata in a physician".

The Qualifications in a Nurse

"Knowledge of nursing, skill, affection for the patient, and cleanliness. These are the tetrad of desiderata in the attendant".

The Qualifications in a Patient

"Recollection, obedience to instructions, courage, and ability to describe his ailment are the tetrad of desiderata in a patient".

Drugs, Their Potency and Sources

"Substances are classified into three groups:

1. Some rectify the discordance of body elements.
2. Some vitiate the body elements.
3. Some are conducive to the maintenance of good health."

"Again, substances can be classified differently in three groups as animal, vegetable and mineral."

"He is the best of physicians who knows the science of administration of drugs with due reference to clime and who applies it only after examining each and every patient individually."

"A drug that is not understood perfectly is comparable to poison, weapons, fire and the thunderbolt, while the perfectly understood drug is comparable to ambrosia. The drug whose name, form and properties are not known, or the drug, which though known, is not properly administered, will cause disaster."

"Even acute poison is converted into an excellent medicine by the right method of preparation. While, even a good medicine may act as an acute poison if improperly administered."

"Therefore, the intelligent man who desires health and long life, should not take any medicine prescribed by a physician who is a stranger to the art of application. One may survive the fall of a thunderbolt on one's head, but one cannot expect to escape the fatal effects of medicine prescribed by an ignorant physician."

"That is the right medicine which makes for health and he is the best physician who relieves people of disease."

"A single drug may have many appellations owing to its diverse actions. If we could indeed find any one drug possessed of all the properties, and capable of meeting all requirements, who would then put himself to the trouble of committing to memory the names and qualities of any other drugs?"

Aims of Therapy

"The physician will try to *cure* the diseases which are curable; adopt *palliative* measures in cases where palliation is the only remedy that can be offered; and *give up* a case which is beyond all medical treatment, and mostly, those which are more than a year's standing".

"The physician who undertakes to treat incurable disease will invariably suffer loss of income, will tarnish his learning and fame, and earn for himself disrepute and taboo in society".

"The curable diseases are of two kinds: those that are easily cured and those that are cured with difficulty. The incurable diseases also fall into two categories: those that are palliable and those that are absolutely irremediable".

Principles of Therapeutics

"That should be known as the proper medication which requires to be taken in small doses, which is quick in action and is curative of even an excessive degree of morbidity, which is easy to take, which is light in digestion, palatable, pleasing, curative of the particular disease, not harmful even if complications arise, not very depressant, and is possessed of the most agreeable smell, colour and taste."

"The physician must take into consideration that drugs differ with respect to land, season, source, flavour, taste, potency, post-digestive effects, and specification, and also that men differ with respect to their body, constitution, age, vitality, gastric fire, morbid tendency, proclivities, homologation and state of the disease."

"An underdose of medication cannot cure the disease just as a small

quantity of water cannot quench a great fire. And medicine given in overdose will prove harmful just as an excessive watering harms the crops. So, after carefully considering the severity of the disease and the strength of the medication, the physician should administer it neither in too large a dose nor in too small a dose."

"The curable diseases, are again classed into three categories by reasons of their requiring mild, moderate or strong treatment. The incurable ones being inexorable, admit of no such classification."

Cautious Therapy

"It is better to take a potion of a mild medication repeatedly as it is attended with only slight discomfort and no risk, than to take a very strong medication which is attended with immediate danger to life".

"The purificatory dose if improperly administered is like poison, and if properly administered, is like nectar."

"All therapeutic measures designed to alleviate disease, however wholesome and however skilfully given, fail to bring about the alleviation of disease if they are used either in insufficient or excessive measure or at the wrong time or in the wrong manner".

"There is no substance which is absolutely of good or bad qualities. Hence our concern should be to select such substances as possess more of the required good qualities".

Approaching Death

"The knower of the medical science should not declare the approach of death, if he is not questioned concerning it, although he clearly perceives the signs prognosticative of the end".

"Even if he is questioned, the physician should not immediately pronounce the prognosis of death where such inconsiderate action on the part of the physician may cause shock to the patient and distress to others".

"While refraining from announcing the approach of the end, the experienced physician should not, however, undertake treatment in a case where he finds that the prognostic signs of death are present".

"But if the physician observes signs which are of a contrary character to those laid down as prognosticative of death, he should certainly declare the approach of recovery as indicated by the auspicious nature of the signs".

Qualities of a Good Physician

"Clear grasp of theoretical knowledge, wide practical experience, skill, and purity of body and mind – these are the tetrad of desiderata of a good physician".

"The physician who possesses knowledge, clear interpretation, right application and practical experience is to be regarded as a the reclaimer of life".

"He who practises medicine neither for gain nor for gratification of the senses, but moved by compassion for creatures, surpasses all".

"Those, who, for the sake of a living, make merchandise of medicine, bargain for a dust of heap letting go a heap of gold".

"There is no benefactor, either moral or material, comparable to that physician who regains those who are being dragged away by fierce disease towards the abode of death, back to life, by severing the noose of death. For, there is no other gift greater than the gift of life".

"He who practises medicine, holding compassion for creatures as the highest religion, is a man who has fulfilled his mission and attains supreme happiness".

"The physician who is endowed with character, intelligence and reason, and has mastered the science of healing, deserves to be venerated as a mentor of all men. He is indeed regarded as Life's guardian, *("Pranacharya")*".

Medical Knowledge & Experience

"A physician well-versed in the principles of Ayurveda but unskilful in his art through want of practice, loses his wit at the bedside of his patient, just as a coward is at his wit's end to determine what to do when for the first time he finds himself in the ranks of a contending army".

"On the other hand a physician experienced in his art but deficient in his knowledge, is condemned by all good men as a quack and deserves capital punishment at the hands of the king".

"Both these classes of physicians are not to be trusted, because they are inexpert and half-educated. They are like a one-winged bird incapable of flight".

"A physician well-versed in the principles and experienced in the practice of medicine is alone capable of curing disease just as only a two-wheeled cart can be of service in a field of battle".

"The endeavours of a man who has studied the entire science but

fails to make a clear exposition of the same, are vain like the efforts of an ass that carries a load of sandalwood without ever being able to enjoy its pleasant scent''.

''For the learned man there are only two methods of examination – direct observation and inference''.

''Practice bestows on a man true insight which leads to success in treatment even as the skill to distinguish between the good and the bad among precious stones is not derived from a mere acquaintance with the theoretical knowledge of gems''.

''A surgeon who is fully conversant with the symptoms which are respectively exhibited by a swelling in its unsuppurated, suppurating and suppurated stage is alone worthy of the epithet. The rest are but impostors''.

''The *Vaidya* who opens up an unsuppurated or unripe swelling out of ignorance, as well as the one who neglects a fully suppurated one, should be looked upon as the vilest *chandal,* for his wrong or incorrect treatment''.

''A patient who is discreet, and is not in a special hurry to end his earthly sojourn, would do well to shun the presence of a bungling, unskilful surgeon who cannot even keep himself unhurt in the course of a surgical operation''.

Physician–Patient Relationship

''The patient, who may mistrust his own parents, sons and relations, should repose an implicit faith in his own physician and put his own life into his hands without the least apprehension of danger. Hence a physician should protect his patient as his own begotten child''.

''No thoughtful man, who seeks enduring life, should ever covet the possessions of the 'guardian of life' or revile him or do any harm to him''.

''Whoever having been treated by a physician does not recompense him whether or not there be a previous understanding for remuneration, that man is beyond redemption''.

''The physician should regard all his patients as if they were his own children and vigilantly guard them from all harm, considering this to be his highest religion''.[4]

Scientific Attitude

''One should not suffer disputants who are of little learning, foolish

and blatant, not because of considerations to oneself, but with a view to keeping the light of knowledge unobscured''.

''Those whose compassion for all creatures is great and who are devoted to truth are ever zealous in putting down false doctrines''.

''The whole of suffering which cleaves mind and body has ignorance for its basis, and conversely all happiness is found in clear scientific knowledge''.

''However, this very knowledge of mighty import is no illumination to those who are devoid of understanding, as is the orb of the sun to those who have lost their eyesight''.

''Of all types of evidence, the one that we observe with the eye is the best''.

''Everything spoken must be supported by reason. Such statements, with their support in reason and clear in their nature, are of use in the science of treatment, for they help to clarify the intellect. The unimpeded intellect achieves the fulfilment of all its efforts''.

Concept of Periodic Health Check up

''The ignorant man fails from stupidity or negligence to note the incipient state of a disease, just as a simpleton fails to recognize a potential enemy.''

''Disease, from atomic beginning, assumes enormous proportions. Therefore, before even diseases show themselves or while yet they are in the incipient stage, one who cares for one's happiness should endeavour to have them treated with proper medication''.

The Ever-sick Patients

''The ever-sick class comprises the priests, the King's officers, the merchant and the courtezan''.

''The priest, engaged as he is constantly in the study and recitation of the scriptural texts, observance of the vows and the daily rites, fails to attend to his bodily good''.

''The King's officer similarly fails in his duty towards his own body by his preoccupation with the gratification of the royal mind, and by the demands made on him by the other dependants of the King, the constant anxiety caused by the various responsibilities of his position, as also the constant fear of incurring the displeasure of his masters''.

"The Courtezan, being dependent on the whims and moods of men, devotes herself to their service and is constantly engaged in acts of toilet and beautification. The merchant is perforce victim to a sedentary mode of life, suppresses the natural urges and can hardly ever afford to have timely meals and exercise".

The Eight Censured Types

"In respect of their bodily conditions, eight kinds of persons are found censurable. They are: the very tall and the very short; the very hairy and the hairless; the very dark and the very fair; the very corpulent and the very emaciated".

"Of these again, the very corpulent and the very emaciated suffer from specially censurable traits; the corpulent person is affected with eight disabilities, viz. diminution of life, lack of agility, difficulty in sex act, debility, fetor, distressing sweats, excessive hunger and excessive thirst".

"Such excessive corpulence is caused by overeating, by the use of articles that are heavy, sweet, cold and unctuous, by lack of exercise, by day sleep, by lack of mental exertion and by inherited tendency".

"That man is spoken of as overcorpulent who on account of the inordinate increase of fat and flesh is disfigured by pendulous buttocks, belly and breasts, and whose increased bulk is not matched by a corresponding increase in energy. Thus, the evils of corpulence together with its causes and symptoms have been set out".

Evils of Emaciation

"The emaciated man cannot stand the strain of exercise or of a full meal or of hunger or thirst, or of disease or of strong medication. Similarly he cannot bear great cold or heat or the strain of the sex act".

"Splenic disorders, cough, wasting, dyspnoea, *gulma,* piles, abdominal affections and disorders of assimilation generally assail the emaciated man".

"That man is said to be over-emaciated who is lean of buttocks, belly and neck, who is covered with a network of prominent vessels, who is reduced to skin and bones and who has prominent joints".

"These two, the very corpulent and the very emaciated, are perpetually afflicted with diseases and are to be treated with constant slimming and nourishing remedies respectively. For reducing the corpulent heavy but non-nourishing food should be given; while for

building up the emaciated, light· but nourishing food should be given''.

''Of the two conditions, emaciation is the lesser evil, though both alike require to be remedied. When both are overcome by disease, it is the corpulent that suffer more''.

''The man is well-proportioned in flesh, well-knit in figure and firm by senses, is not overpowered by the violence of disease. He is able to endure hunger and thirst, heat and cold and the strain of exercise, and has normal digestive and assimilative powers''.

Assessment of Fatal Prognosis

''Just as the blossom is the harbinger of the coming fruit, so is the evil symptom known as fatal prognosis the harbinger of the death of the patient. The appearance of fatal symptoms never ends except in death and there is no death that is not preceded by the appearance of fatal symptoms''

''The ignorant are deluded into mistaking for fatal symptoms what are not such, and the really fatal symptoms go unrecognized by them. This is the result of delusive knowledge.''

''That man is regarded by the wise as manifesting fatal symptoms, who exudes day and night, smell, resembling those of various flowers in a forest abounding in various trees and creepers bursting into bloom. Such a man is certain to die before a year.''

''A man whose body exudes a mixture of unpleasant smells, or a single unpleasant smell, is to be regarded by the physician as one showing fatal prognostic symptoms.''

''Flies, lice, wasps and mosquitoes get repelled and turn away from the bad taste of the body of the man about to die.''

The Method of Investigation

''The physician should palpate the patient's entire body with his hands which must be in a normal condition. While feeling the patient's body the following are the abnormalities to be noted.''

''They are:—the absence of throbbing in those parts which are always throbbing; coldness of those parts which are always warm; rigidity of those parts which are always soft; roughness in those parts which are always smooth; the disappearance of those parts which should normally exist; the looseness, sagging or dislocation of joints;

the paucity of flesh or blood; hardness; excessive perspiration; also whatever else that is abnormal and unaccountable."

"If the patient's respirations are either too long or too short, it is to be concluded that he is nigh unto death. If the two sides of the neck, on being felt, are observed not to pulsate it is to be concluded that he is nigh unto death. If the patient's eyes are not normal but evince abnormal tendencies, that is to say if they are too protuberant, too sunken, too oblique, too asymmetrical, either perpetually open or perpetually closed, then it should be concluded that the patient is near death's door."

"If the physician tugs at a few hair on the head or body and they come out with the roots without causing pain, then it is to be known that the patient is soon to depart from life."

"If the veins in the abdominal region become conspicuous, it is to be understood that the patient is not going to survive".

"If the nails are drained of blood, or if they look dark blue resembling the colour of ripe fruits of the jambul tree, it is to be gathered that the patient's days are numbered".

"If a debilitated patient develops abdominal distension and diarrhoea, his life is difficult to save".

"If constipation and excessive thirst make their entry into an already weakened man, life deserts him ere long".

"A full conception of the science will never be attained by the knowledge of only a part of it".

"Thus believing to have a perfect approach to the whole subject by the knowledge of one branch only, the physician blunders".

"Those who are mistaken in the diagnosis of disease will also be misled in deciding the line of treatment".

"Being deluded by a misconception of the nature of the disease they administer wrong medication, which either kills the patient or brings down upon him greater affliction".

"The physician, knowing all that is to be known, examining everything in every respect possible and diagnosing after full investigation, will never be mistaken and will be able to achieve the desired result".

"There is no limit at all to the Science of Life; so you should apply yourself to it with diligence. The entire world is the teacher to the intelligent and the foe to the unintelligent. Hence, knowing this well,

you should listen and act according to the words of instructions of even an unfriendly person when they are worthy''.

The first "flame photometer"

''In case of suspected poisoning of the food, the physician should throw part of it in the fire. The fire burns abnormally when food containing poison is cast into it. The flame becomes variegated in colour like the feathers of the peacock and the smoke is acrid, intolerable, dry and smells like a corpse''.

The first Urine specific gravity test

Nagarjuna has described *"Taila Bindu Pariksha"* or oil drop examination. A drop of ''til'' (sesame) oil is gently placed with the help of a hay stick, on the surface of urine collected in a utensil. If the oil spreads over the surface, the disease is curable. If the oil drop remains suspended, the disease is difficult to cure. If the oil drop settles to the bottom, the disease is incurable.''

In praise of discussion

''Discussion with a person of the same branch of Science is indeed what makes for the increase of knowledge and happiness. It contributes towards the clarity of understanding, dispels doubt and confirms the ideas of those that have no doubts. It enables one to learn new things in the course of the discussion''.

''One should persuade gently and in a spirit of goodness. One should not rejoice in the discomfiture of the other party in a discussion. One should not boast before others. One should not get deluded by a partial or imperfect grasp of the subject. One should not expatiate on what the other is not at all acquainted with''.

''Before the assembly of unfavourably disposed persons, one should not engage in debate under any circumstances and with anyone, whether such assembly be composed of men of learning, experience and dialectical skill of statement and rejoinder, or of ignorant persons''.

''In a hostile debate one should speak skilfully and never object to statements backed by authority. The hostile debate which is serious, enrages some people. And there is nothing that an enraged man may not do or say; and the wise never commend a quarrel before an assembly of good men.''

"Excellence of speech is that which is neither insufficient in sense nor superfluous, which is full of meaning and not delusive, nor self-contradictory and which is explicit in sense."

"Everything spoken must be supported by reason. Such statements with their support in reason and clear in their nature, are of use in the science of treatment, for they help to clarify the intellect. The unimpeded intellect achieves the fulfilment of all its efforts."

Chapter 2

THE SCIENTIFIC METHOD IN MEDICINE

Introduction

The World Health Assembly in 1977 evinced considerable interest in traditional systems of medicine and their promotion and development; the need to evaluate and validate their therapeutic claims on modern scientific principles was emphasised. Such efforts were already initiated in free India in the 1950's. After visiting the Central Institute of Research in Indigenous Systems of Medicine at Jamnagar on 2nd November, 1955, Pandit Jawaharlal Nehru, the first Prime Minister observed:......."a fascinating inquiry is going on in this research institute and it may well lead to very fruitful results. The only right approach has to be one of Science, that is, of experiment, trial and error. In whatever type of medicine we may deal with, we cannot profit by its study unless we apply the methods of science. Nothing should be taken for granted. Everything should be tested and proved and then it becomes a part of scientific medicine – old and new."

John Dewey wrote that the future of our civilization depends upon the widening spread and deepening hold of the scientific habit of mind. The problem of education is to discover how to mature and make-effective this scientific habit.

All of us enjoy the fruits of science. Most of us accept the facts of science. However, very few of us have assimilated the spirit of science.

It would therefore be very essential and very appropriate to begin with a discussion on the scientific method and its application to Medicine.

What is this thing called Science?

Man is a rational animal, hence he constantly seeks to understand the phenomena around him, to find a cause-effect relationship of events

and happenings in and around him. The search for meaning, search for establishing a causal sequence, especially if anything has to be done about it, is the stimulus for science. The questions *"what? where? how* and *why?"* are being asked constantly and sought to be answered by science, which is a system of accurate and related knowledge.

Francis Bacon, in the early 17th century was among the first to attempt to articulate what the method of science is. He proposed that the aim of science is to improve man's lot on earth, and for him that aim was to be achieved by collecting facts through organized observation and deriving theories from them, which have the ability *to explain* and *to predict.*

The intellectual process by which singular statements that result from observations are turned into universal statements or theories is called *induction.* The intellectual process by which theories are applied to predict observations not yet made is called *deduction.*

Science is a structure built on facts. Scientific knowledge is proven knowledge, hence reliable knowledge; it is objective and verifiable knowledge. In essence, the scientific method consists of careful observations of nature and cautious confirmations of all conclusions, to the exclusion of unsubtantiated hypotheses – to search out and study the secret of nature by way of experiment. Endeavour of Science has been to bring man's study of Nature into the realm of rational and experimental analysis away from the supernatural.

It is essential to understand science as a *historically evolving body of knowledge.* Observation and experiment are the methods of science. As new observations are added to the total body of scientific knowledge some of the older observations lose their relevance and become obsolete or their significance is altered. This dynamic aspect of science is perhaps its most outstanding attribute.

The number of scientific "facts" keep on growing at an increasingly rapid rate and the progress in scientific thought is many times achieved at the expense of previously held beliefs. A constant re-examination of every "fact" or "theory" is the essence of science. No belief is held too sacred to be questioned. No authority is considered above the need for evidence to support its contention.

Scientific truths are "contemporary truths" rather than "eternal truths". "Final truth" does not seem absolute in science. The answer to one question invariably brings into focus more questions which were not apparent before, thus the quest of science is in the sense of a

horizon towards which one may proceed rather than a point which may be reached.

The Scientific Method

Certain ways of looking at things and doing things characterize all the sciences. It will be worth understanding these characteristic features of the scientific method.

The scientific method essentially consists of four steps: (1) Observation, (2) Hypothesis formulation, (3) Hypothesis testing by experiment and (4) Induction – derive general principles from observations, and apply these principles to make predictions.

Observations or Empiricism

In science, facts are gathered by systematic observations. No reliance is placed on intuition, opinion, or belief. Much of our knowledge in medicine has been gathered, from the times of Charaka, Sushruta and Hippocrates, right into the present time, by the method of systematic observations.

Observations may be made by the scientists themselves or they may have been made by others and accepted by the scientist after he has satisfied himself about their validity. Many drugs and practices from folklore have entered the corpus of scientific medicine by this channel.

Observations may relate to phenomena occurring spontaneously in nature, or the observations may be made under controlled experimental conditions in a laboratory. Observations may be made by chance or by plan. During experimentation, unforeseen or unexpected observations should not be neglected merely because they appear confusing or irrelevant. It is often the unexpected which shows the way to a new discovery. Many discoveries are made by chance; but as Pasteur has said, "In the field of observation, chance favours only the prepared mind."

Measurement is another distinguishing feature of science. Lord Kelvin had stated: "If you can measure what you are speaking about, if you can express it in numbers, you know something about it. But if you cannot measure it, cannot express it in numbers, then your knowledge about it is of a meagre and unsatisfactory kind."

Biological phenomena show a great deal of variability, descriptive statistics – the mean, the median, and standard deviation and standard error of measurement, help to characterize a group of scores or

measurements. Correlations tell us whether two sets of measures relate to each other. Inferential statistics help us decide whether differences obtained, between experimental groups are *real* or only the result of *chance variations*.

Careful *definition* of terms is essential to clear thinking in science. The trick in science is to define concepts by relating them to something that is observable, and better still, measurable. A major hurdle in any research effort in Ayurvedic concepts is that *"Vata"*, *"Pitta"* and *Kapha"* do not lend themselves to measurement.

Hypothesis formulation

Whatever way observations are made and validated, the scientists try to *systematize* their observations and experiments, "to make some sense." They try to derive *general principles* from their observations. The intellectual process in science, that enables *singular statements* that result from observations to be *universal* statements, is called *inductivism.*

The inductive process of science must satisfy several conditions for generalizations to be legitimately made from singular statements.

1. The number of observations forming the basis of a generalization must be large. We should not jump to conclusions.

2. The observations must be repeated under a wide variety of conditions.

3. No accepted, observed statements should conflict with the derived universal law.

The difficulties associated with the justification of induction have been discussed by Karl Popper as the "problem of induction". How large should be the number of observations? The destructive effects of the atom bomb were based on just one dramatic observation.

In general, the greater the number of observations forming the basis of an induction, and greater the variety of conditions under which these observations are made, the greater the *probability* that the resulting inferred generalizations are true. Scientific knowledge thus represents knowledge that is probably true.

How varied should be the circumstances under which observations are to be made? The variations that are significant are to be distinguished from those that are superfluous, by appealing to our theoretical knowledge of the situation, which implies that *theory plays a vital role prior* to observations.

Fallacies of Induction and Deduction

Induction is the process of drawing general conclusions from particular instances. It is a basic process whereby learning takes place. For instance, consider the reproduction of birds: Chickens lay eggs, robins lay eggs, ostriches lay eggs and so on, and thus we generalize that *all* birds reproduce by laying eggs. We have not proved this conclusion, however, because we have not studied all the birds, and there is always a theoretical possibility that a contrary example will be found. For this reason inductive reasoning cannot lead to indubitable truth; it is only the likely or probable truth.

Deduction is another matter. Given true premise, a conclusion reached by valid deduction must be rigorously true. For instance, consider this syllogism.

A. If it is raining, the streets will be wet.
B. It is raining.
C. Therefore the streets will be wet.

Now consider the converse.

A. If it is raining the streets will be wet.
B. The streets are wet.
C. Therefore it is raining.

The fallacy is obvious. After all, the streets could be wet for *other* reason than rain.

The most appropriate reasoning in science is based on the *hypothetico-deductive method:* the testing of a hypothetical model which attains even more convincing likelihood as it passes each test successfully.

To overcome the problem of induction, Karl Popper proposed the *falsificationist* approach. The falsificationist freely admits that observation is guided by and pre-supposes a theory. Theories are constructed as conjectures and guesses, freely created by human intellect to understand the world around us.Observations and experiments are *guided by a theory* or *working hypothesis;* they are never made in a vacuum; they are made to *test* or shed light on some theory. Theories are verified, or improved, or extended, or rejected by observations and experiments.

Science progresses by trials and errors, by conjectures and refutations. Only the fittest theories survive, on the criteria of *testability, reproducibility* and *falsifiability.* Popper emphasises the importance of falsifiability. Many religious, social and psychological theories are unfalsifiable. As an illustration, a horoscopic prediction, "Luck is possible

in sporting events" is an assertion which is unfalsifiable. Fortune-tellers and politicians can avoid being accused of making mistakes or breaking promises by making their assertions so vague that they can always be construed as compatible with whatever may happen. Any theory or hypothesis is falsifiable if there exists a logically possible observation statement, or set of observation statements that are inconsistent with it, that, if established as true, would falsify the hypothesis.

In science a working hypothesis or a model is revised or abandoned when it fails to account adequately for all the observed data.

A *dogma*, on the other hand, requires that discrepant data be forced to fit the model, or be excluded, or ignored, or suppressed deliberately.

Intuition and Imagination

The creation or birth of an idea is purely intuitive. It is not something that we do, it just happens. New ideas and theories are conceived in a variety of ways. They may occur to the discoverer in a *flash of inspiration* (like Newton's law of gravitation being triggered by observing a falling apple from a tree), or *an accident* (like the discovery of X-rays by Roentgen, or the discovery of ratioactivity by Becquerel), or by a long series of *observations and calculations* (like Kepler's laws of planetary motion).

Einstein once wrote – "There is no logical way to discovery of these elemental laws. There is only the way of intuition, which is helped by a feeling for the order lying behind the appearance."

The scientific method is concerned with events *after* the birth of an idea. The idea is the seed; the scientific method provides the conditions for it to bear fruit, if any. Rational faculties are employed in verifying, interpreting, developing and building the theoretical structure around the original idea. Rational faculties are also necessary to sit on judgement to decide the value and viability of the idea itself.

Claude Bernard, in his "Experimental Method in Medicine", wrote: "we usually give the name of discovery to recognition of a new fact. But I think that the *idea* connected with the discovered fact is what really constitutes the discovery. Facts are neither great nor small in themselves. A great discovery is a fact whose appearance in science gives rise to ideas shedding a bright light which dispels many obscurities and shows us new paths. There are other facts which although new, teach us but little; they are therefore small discoveries.

Finally there are new facts which although well observed, mean nothing to anyone; they remain, for the time being, detached and sterile in science; they are what we may call crude or raw facts."

Curiosity provides the stimulus for the production of ideas. Curiosity prompts us to ask questions and explore further. There is no limit to the curiosity of a scientist. As Einstein said, "He who cannot wonder, cannot feel curious about things around him, is as good as dead, a snuffed-out candle."

Imaginative thinking is one of the most important tools of research. The greatest advances are made through the boldest and most imaginative hypotheses. However, imagination must be coupled with insight, for the success of any outstanding hypothesis. Theories without facts to support them are more useless than facts without theories to correlate them.

Scepticism is an important quality in which a scientist differs from a layman. The scientist is trained not to take things for granted without validation by the scientific method. Human gullibility and unquestioning faith in authority was the reason why Aristotelian and Galen's theories held a complete sway over human thought for over a thousand years. Hence Galileo had to assert: "In the discussion of natural problems we ought not to begin with the authority of the Scriptures, but with sensible experiments and necessary demonstrations."

On the other hand scepticism to fruitful ideas has also been equally prevalent in the history of science and has delayed many useful discoveries; I have given several examples in this book.

Curiosity to examine with an open mind any idea or any proposition, and scepticism in its acceptance unless valid proof is provided in its support make an ideal blend in a scientific mind. One is thereby safeguarded against lost opportunities and false hopes. Uncritical acceptance and uncritical rejection of an idea or proposition are both equally inimical to the spirit of science and to scientific advancement.

It is quite natural for the unenterprising intelligent to find a comfortable security and serenity in a set of conventional opinions which have been satisfactorily pre-arranged. The unusual is promptly dismissed because it does not fit into the established plan. It is important to keep our minds open and recipient, hospitable to new ideas and fresh advances, provided validation comes forth in their support. "Give me a fact", said Carlyle, "and I will prostrate myself before it." Hypotheses pass, but facts remain. Theories may be controversial, facts can be disputed by no one.

Hypothesis construction is the most creative aspect of a scientist's work, and designing experiments to test the hypothesis is the most challenging. Hypothesis is a statement or a proposition suggesting a correlation of facts or observations. It is only a tentative answer to a question or a provisional explanation for a problem.

It is important for a scientist not to be *biased* by the choice of one hypothesis to the exclusion of every other possibility. It is important to have a working hypothesis in the light of which observations can be related to one another. At the same time one should note and consider all possible alternative hypotheses before subjecting one hypothesis to experimental verification. Considering multiple hypotheses helps to keep one's mind open to explanations other than those which are being considered at any given time.

Experimentation

The object of experimentation is to validate and prove the truth of a hypothesis. Any hypothesis that cannot be subjected to test by experiment, cannot be a subject of scientific inquiry. As Popper has emphasised, *testability, verifiability* and *falsifiability* are necessary attributes for any hypothesis to be subject of scientific inquiry.

In an experiment it is important that only the variables are allowed to change. Factors other than the independent variables which might affect the dependent variables must be held constant. It would be no good to study the effects of varying an independent variable if other factors, unknown to the experimenter, changed also. *Control* is therefore an important characteristic of the experimental method. Two main strategies are used to control extraneous factors; one strategy employs control groups; in the other, each subject serves as his own control. Ideally we want a control group which is *matched* with the experimental group in every relevant way except the independent variable. An experiment is no better than its controls.

The essence of the scientific attitude is *objectivity*. Experimenters' *bias* must be eliminated while making observations. Methods are available to ''blind'' the experimenter; for instance in a drug trial the experimenter is kept in the dark about which group is receiving the active drug and which group is receiving a ''dummy tablet'', while he is observing the effects on the patients. In some experiments each subject can act as his own control, a baseline being established before introducing the independent variable, in a *before and after* experiment.

Reproducibility and repeatability are important aspects of the experimental method – It is important to appreciate that hypotheses are many times accepted merely because they are *plausible,* and with the passage of time they come to be regarded as *"facts"* even if not a shred of sound evidence was ever produced to give support to them. Once this happens, it is very difficult to root them out. This difficulty is constantly encountered in a scientific study of "Vata", "Pitta" and "Kapha", in relation to cause and cure of disease.

Experiments are nothing but observations carried out under controlled conditions. The experimenter changes or varies something, keeps other conditions constant, and looks for an effect of the change or variation upon the system he has under observation,

Variables in science are things which are measurable and quantifiable. Variables may be either independent or dependent. An *independent variable* is a condition set or selected by the experimenter – a drug administered or a stimulus presented etc. The *dependent variable* is a measure of the response. The dependent variable is so-called because its value depends, or may depend, on the value of the independent variable – the one independently set by the experimenter. In every experiment we must have at least one independent variable and one dependent variable. It is possible, with appropriate experimental design, to have several independent variables and several dependent variables in the same experiment. Not only is it essential that you can repeat and reproduce your results, but that others using similar experimental conditions, should be able to do so. Things which happen *once only* and cannot be repeated or reproduced, belong to the realm of "miracles", and not science.

Science and Logic

A major feature of science is its ability to *explain* and to *predict.* For instance, given the theory that metals expand when heated, it is possible to *derive* the fact that continuous railway tracks not interrupted by small gaps will become distorted in the hot sun. This is *deductive reasoning.* A study of deductive reasoning constitutes the discipline of logic. All that logic can offer in this connection is that *if* the premise is true *then* the conclusion must be true. But whether the premise (or initial condition) is true or not, is not a question that can be settled by an appeal to logic. Deductive logic alone, then, does not act as a source of true statements about the world. Deduction is only concerned with

the derivation of a statement from other initial statements. For instance if the initial statement or premise is that a person has fits or convulsions because he is possessed by demons, then beating, branding or other torture inflicted on the patient's body to force the demon to leave, is a "logical" treatment! In medical thinking logic is extensively used for deductive thinking. The fallacies of deductive thinking have been pointed out on an earlier page.

A priori deduction works from cause to effects, for example, this disease, therefore look out for these consequences.

A posteriori deduction works from effect to cause for example, these symptoms, therefore this disease.

Logic based on incomplete knowledge of facts is always treacherous.

Science and Meta-science

Human mind is always curious about "How" and "Why". Science often confines itself to "How" and avoids the "Why" which belongs to philosophy. Science only tackles *answerable questions* which are within the capabilities of the scientific method. The scientists' approach is typified by the following comments by Louis Pasteur: "It is time that I freely put myself away from ideas which cannot be vigorously tested and proved; that is my way of looking at things".

Human intelligence has devised many useful and attractive concepts which however, cannot be the subject of scientific inquiry. The concept of Heaven and Hell is a good example. The lure of heaven and the fear of hell have kept many people on the straight path of virtue, just as the carrot and the whip keep the donkey going. The ancient Indian concept of "*karma*" is also an attractive one. But these concepts cannot be tested by science because, in the words of Karl Popper, they are not testable, verifiable and falsifiable. The unwillingness of scientists to tackle concepts or subjects outside their scientific method does not imply their denial of existence of reality outside the scientific method. This self-imposed limitation of science precludes the discussion about spirituality, although, as Pandit Nehru once said, the future of mankind will depend upon a good blend of science and spirituality.

The strength of Science is its ability to tackle answerable questions. It is by this approach that science made progress through men who separated answerable physical questions from unanswerable metaphysical questions, while philosophy remained relatively stagnant.

The great difference between Science and Religion is the readiness of

science to accept change. It is very difficult for the ardent believer in religion to budge from a stand that his forebears had taken up in the past. There are no "conscience values" attached to scientific beliefs. They can be cheerfully accepted, modified or given up to accommodate newer findings offering more cogent and consistent explanations of the phenomena under observation or investigation. This free-thinking approach of science often brought it into conflict with religion.

Copernicus pointed out that the earth is not the centre of the universe; Galileo saw stars and planets but not angels in the sky; Darwin showed that man is related to all other living organisms; Einstein introduced new notions of time and space, and of mass and energy; Watson and Crick showed that biological inheritance can be explained in physical and chemical terms; all these examples illustrate the endeavour of science to bring man's study of Nature into the realm of rational and experimental analysis, away from the supernatural.

Limits to Science

Werner Heisenberg has said "Every word or concept, clear as it may seem to be, has only a limited range of applicability. Scientific theories can never provide a complete and definitive description of reality. They will always be approximations to the true nature of things. Science advances through tentative answers to a series of more and more subtle questions which reach deeper and deeper into the essence of natural phenomena."

Any one who explores nature always wonders about the *why* of the *what* he observes. Yet he seldom can find out why, and when he does, each answer raises a new series of questions. Because the sequence of questions is endless, scientists cannot find ultimate answers for the why's of nature's manifestations. After a certain stage in the questioing the matter reverts to *philosophers* or *theologians* who seldom provide unanimous replies.

Claude Bernard, who so keenly looked for causes of natural phenomena, was willing to settle for a satisfactory "how". He regarded his scientific objective as "defining the conditions necessary for the appearance of the phenomena". He said: "The nature of our mind leads us to seek the essence or the "why" of the things.......but experience soon teaches us that we cannot get beyond the "how". If our feeling constantly puts the question *why,* our reason shows us that only the question *how* is within out range." This is true of all experimental

sciences in which we reach only relative or partial truths, but this knowledge is enough to broaden our understanding and our power over nature.

Application of Science to Study Life Processes

Rene Descartes, usually regarded as the founder of modern philosophy, in his famous book, "Discourse on the method of rightly conducting one's reason and searching the truth in science", emphasised the method of radical doubt and analysis of a problem into its components.

Rene Descartes' approach to the study of living organisms has had a decisive influence on the development of life sciences. Clock-making had attained a high degree of perfection in Descartes' time, and Descartes thought of the analogy of the working of the clock to the working of the human body. Descartes explained at great length how the motions and various biological functions of the body could be reduced to mechanical operations. "We see clocks, artificial fountains, mills and similar other machines, which though merely man-made have none-the-less the power to move by themselves in several different ways....I do not recognize any difference between the machines made by the craftsman and the various bodies that Nature alone composes".

"I consider the human body as a machine; my thought compares a sick man and an ill-made clock with my idea of a healthy man and a well-made clock". It must be appreciated that the careful description of the mechanisms that made up the living organism has been a major task achieved by biologists. The main challenge science is still left with is the brain and the question whether or not it is something more than a machine of vast and magnificent complexity is still not fully answered.

It is worth noting that Descartes, while recommending the mechanistic approach to the study of the human body, suggested that *the way to study the mind was by introspection.* The Cartesian division between mind and body has been criticised by many modern critics of medicine as the main reason for preventing doctors from understanding many of today's major illnesses. Fritjof Capra, in his book "The Turning Point – Science, Society and the Rising Culture" has pointedly criticised the Cartesian model of thinking, which criticism to my mind, is largely unjustified. One of the real impediments to progress in

biology and medicine till the pre-modern times was the generally held notion that living systems did not need to follow the laws of physics. *Vitalism* was a major conceptual obstacle on the road to enlightenment. We owe it to Descartes that the laws of physics and chemistry could be applied to the study of biological phenomena. The proof that living organisms obeyed the laws of thermodynamics with respect to the transformation of energy was very important to the whole philosophical basis of modern biology. From an erstwhile basis of speculative philosophy medicine became an observational science subject to experimental verification with the application of the Cartesian approach.

The criticism that the reductionist, analytical approach of the scientists makes them lose the ability to understand the coordinating activities of the whole system is in my opinion totally erroneous. In fact, an analytical approach facilitates a more meaningful synthesis. Paul Weiss has put it well: "There is no phenomenon in a living system that is *not* molecular; but there is none that is *only* molecular either."

Experimental Method in Medicine

Astronomy is a good example of a science which is essentially observational. The physical sciences, physics and chemistry advanced mainly because of the experimental method. In biology and medicine the experimental method arrived relatively late. It started with vivisection and experiments on animals. Claude Bernard was perhaps the first medical person to use the experimental approach consistently and establish it as an invaluable aid in studies on physiology.

The experimental method is the most efficient and productive method of discovering new knowledge. In the observational sciences there is often no control over the time element. For instance it will take several years or decades to study the natural history of diabetes mellitus in a given population of diabetics. In spontaneous animal models of diabetes or in experimentally induced animal diabetes this period can be reduced to a few months or one or two years. Furthermore, various parameters (variables) can be controlled and studied and effects of therapeutic interventions observed on each one of them independently – an opportunity that is rarely available in studying human diabetes.

The most frequently used animals in experimental medicine are mice, rats, guinea pigs, rabbits, hamsters, cats, dogs, sheep and goats,

pigs and monkeys. Study of experimental diabetes, obesity, hypertension, Cancer and autoimmune disease, among others have provided great insights into the understanding of human disease. For teaching and training in surgical skills, larger animals like dogs and cats are used.

Scientific Study of Symptoms & Signs

Since ancient times patients have presented to physicians with symptoms and signs as expressions of their illness. These evidences of illness have not changed much over the centuries, but our insight into what these evidences represent has changed greatly. As our knowledge about the mechanisms of a disease process unfolds, the significance of its symptoms and signs, becomes clearer. Symptoms are meaningful to the extent we know what significance to attach to them. The clinician with the most insight into the pathophysiological processes of illness is best equipped to help the patient by providing a correct analysis and interpretation of symptoms and signs.

Epilepsy provides an interesting example to illustrate the evolution of our knowledge regarding the meaning of symptoms. Hippocrates provided the first rational and scientific approach to epilepsy. Hippocrates, like Charaka and Sushruta, believed that knowledge comes only from direct observation. "I am about to discuss epilepsy, the disease called 'sacred.' It is not in my opinion any more sacred or any more divine than other diseases but has a natural cause, and its supposed divine origin is due to men's inexperience and to their wonder at its peculiar character."

It was reasoning from clinical observations that gave neurologists their first inkling of the localization of function in the brain and the site of origin of epilepsy. Hughling Jackson in 1870, from the study of certain cases of epilepsy following lesions in the brain, concluded that the symptoms could best be explained by the assumption of functional localization, the epileptiform convulsion being the result of irritative lesions on the contra-lateral side.

Following the advent of EEG (electro-encephalography) Hans Berger in 1929 showed the important contribution of electrical brain waves in the diagnosis of different types of epilepsy and to locate the focus in the brain causing the trouble. In experimental animals and human beings, grand mal convulsions can be initiated by administering neuronal stimulants such as metrazol, or by insulin-induced hypoglycaemia (blood sugar level below 50 mg %), or by the passage

of alternating electrical current directly into the brain. Electrical recordings from the thalamus and also from the reticular formation in the brain stem, during grand mal attacks show typical high voltage activity in both of these areas similar to that recorded from the cerebral cortex. Furthermore, in an experimental animal, even after transecting the brain stem as low as the mesencephalon, a typical grand mal seizure can still be induced in the portion of the brain-stem below the transection.

Presumably therefore, a grand mal convulsion is caused by intrinsic over-excitability of the neurons that make up the reticular activating structure, or from some abnormality of the local neuronal pathway.

Electrical stimulation of the human cerebral cortex carried out by Penfield and Jasper in the course of surgical operations on the brain have provided a wealth of information regarding the functional localization in the brain, thus facilitating the correlation of symptoms to the underlying neuropathology, especially in temporal lobe epilepsy.

Experimental Study of Pain

Pain is the most common symptom that brings a patient to a physician, and in the last few decades various experimental methods have been used to understand pain mechanisms and to induce pain and quantitate it so as to enable comparative assessment of pain-relieving measures (analgesic drugs, acupuncture, hypnosis etc). One limitation of experimentally induced pain as opposed to spontaneous pathological pain is the absence of the anxiety component (e.g. chest pain associated with anxiety about possible sudden death from heart attack, pain of snake bite associated with anxiety of death from poisoning).

Harold Wolff and his associates have extensively investigated the mechanism of pain in various types of headache. In the study of migraine, for instance, histamine-induced headache has been used as a model to demonstrate vasodilatation as a mechanism of pain. Several lines of evidence suggest that serotonin may play a role in the migraine syndrome. Reserpine, which induces a drop in serum serotonin levels, will often induce a migraine attack; serum levels of serotonin have been found to drop spontaneously just before a migraine attack. Methysergide, a powerful serotonin antagonist, prevents or reduces the frequency of migraine attacks in most subjects.

Cardiac pain has been experimentally studied and the current theory has arisen out of the experimental work of Lewis, Pickering and

Rothschild. They applied pressure to an arm by a blood pressure cuff and noted the occurrence of pain within 70 seconds after exercise of the arm was begun. Similar occlusion of the resting arm was not followed by pain despite the development of intense cyanosis. They concluded that during ischaemic muscular contraction a substance is produced which causes pain, and that anoxaemia alone does not produce pain. Katz and his associates pursued this idea further and presented striking evidence that a substance (or substances) produced during muscular contraction, accumulates in the presence of ischaemia (poor blood supply) and anoxia (lack of oxygen) and provokes intolerable pain. Angina pectoris and intermittent claudication were attributed to this mechanism.

Oxidative processes within the heart muscle consume glucose, fatty acids, lactate and amino-acids. The final utilization of these fuels is in the Kreb (tricarboxylic acid) cycle which takes place in the mitochondria of the cardiac muscle cells. In the hypoxic state pyruvate derived from glucose is converted to lactate and is metabolised no further. Ischaemic areas of myocardium have been distinguished by excessive quantities of lactate in the coronary vein.

Experimental Study of Emotion-induced Symtoms

In 1897, when Walter Cannon was using the then recently discovered X-rays to study the movements of the stomach, some animals showed the rolling waves with utmost definiteness while others showed no movement whatsoever. After some time he noted that the absence of motility was accompanied by signs of perturbation in the animals and that when serenity was restored the waves promptly reappeared. This observation lead to a long series of studies on the effects of strong emotions on bodily function. The opportunity of observing patients with gastric fistula (Beaumont, Carlson and Wolff and Wolff) vividly showed the changes in the motility and vascularity of the gastric mucosal lining in response to changing emotions. These and other studies brought a better understanding of the symptomatology of emotionally-induced alteration in gastro-intestinal function (cardiospasm, anorexia, pylorospasm, nervous diarrhoea, irritable colon, etc.)

Science of Medicine and Practice of Medicine

Sir William Osler had described medicine as a science of uncertainty and an art of probability. Throughout history, the practice of medicine

has always lagged behind the science of medicine. To my mind the greatest change in the 20th century has been the inculcation of scientific objectivity and criticality in the clinical practice as a direct result of the impact of *clinical science.* Today clinical medicine finds a close integration with basic sciences as never before. Recognition of *clinical investigation* as a branch of science, and the *clinical investigator* as a new kind of scientist, is relatively recent. The 25 years following the Second World War witnessed an exciting and unprecedented growth in clinical research. During this period clinical science matured as a full-fledged branch of the biological sciences. Clinical investigation has evolved into the most complex of all branches of biology. Clinical investigators avail themselves of the vast technology of basic biology, the physical sciences and the social sciences. Flow of idea from the clinic to basic biology and the reverse flow of information from basic biology to clinical medicine have enriched both fields. At the bedside the clinical investigator picks up unsolved problems, particularly the unusual or atypical patient problems which may offer research opportunities. William Castle used to say that the role of the clinical investigator is to ask the question at the bedside and then go as far from the bedside as his curiosity, legs, money and facilities will take him. Some may take one step, some may take ten, but the important thing for the clinical investigator is the direction he walks, not the number of steps he takes.

Scientific evaluation of therapy is discussed in a separate chapter. Before the impact of clinical science, the practice of medicine was deplorably uncritical, anecdotal, ineffective and sometimes harmful. A lot of drugs and mixtures were over-used with little or no supporting evidence of rational practice. The critical approach of clinical science has led to the curtailment of many forms of therapy that are without value. Eternal vigilance will be needed to prevent newer forms of useless therapy from creeping into medical practice. Self-imposed quality assurance programmes in delivery of medical care, controlled clinical trials, careful investigations on *safety* as well as *efficacy* of medical technology, serious considerations of cost-effectiveness, cost-benefit analysis and social benefits of medical technology, are activities which reflect the scientific temper of modern medicine.

But medicine is an art as well as a science and the important note on which I would like to conclude this chapter is that scientific approach to medicine is not inimical to humane approach to patients. To suggest that they are mutually exclusive is utterly erroneous.

Chapter 3

SCIENTIFIC EVALUATION OF THERAPY

Introduction

In December 1977, a WHO meeting was held in Geneva to evolve a plan of action to promote and develop the various aspects of traditional medicine. It recommended research and studies in traditional medicine with a view to *assessing its therapeutic claims* and *validating them on scientific basis.*

Charaka Samhita states that the physician, the drug, the attendant and the patient constitute the four basic factors of treatment. Therefore in the scientific evaluation of any form of therapy one has to take into account these four factors.

The care of a patient begins with the development of a personal relationship between the patient and the physician. The *belief* on the part of the patient that the physician is *competent* in his work and that he has *superior knowledge* about the illness and its treatment, and that *the treatment he is giving is going to benefit the receiver,* is one of the most important determinants of the outcome of therapy. Charaka was fully cognizant of this fact, and in order to reinforce the belief of the patient in the therapy given, he enjoined on him chanting some sacred hymns, while taking the drug. "If a person, after cleansing the mind of its impurities like passion, doubt or other inauspicious sentiments, and concentrating his mind on the treatment, takes this dose, it brings about the most desirable results".

Charaka was thus aware of the *patient's expectation* as a crucial ingredient in success of any therapy.

In the absence of trust and confidence on the part of the patient, the effectiveness of most therapeutic measures is diminished. In the practice of medicine fortunately, a large majority of complaints and illnesses are *self-limiting,* and in most instances, where there is confidence

in the physician, *reassurance* is the best treatment and often, is all that is required. Likewise, in those cases which do not lend themselves to easy solutions or for which no effective treatment is available, the patient's belief that the physician is doing all that is possible is one of the most important therapeutic measures that can be provided.

In 1785, Benjamin Franklin led a commission to investigate Mesmer's "animal magnetism", and in series of elegant experiments showed that the subject's imagination was the most important factor in explaining the bizarre effects and miraculous cures attributed to that practice. Physicians were not reluctant to take advantage of the *power of imagination and expectation* to change bodily state and to cure illness, by prescribing medication thought to be pharmacologically inert when no specific remedy was indicated or was available. Thomas Jefferson wrote to his doctor in 1807, "one of the most successful physicians I have ever known, has assured me that he used more of bread pills, drops of coloured water and powders of hickory ash, than of all other medicines put together".

Placebos and Placebo Effects

A *placebo* is an inert substance, devoid of any pharmacologic actions, but may be given to a patient who believes that it is an active drug. The contemporary era of placebo research began with the adoption of the experimental method of evaluation of therapy—the double-blind controlled trial—to be discussed in a subsequent section of this Chapter. Placebo research has brought out convincingly the contribution made by the *patient's belief,* in his recovery. Chalmers has reported a study on the role of ascorbic acid (vitamin C) in cold prevention. The group on placebo who thought they were receiving ascorbic acid had fewer colds, than the group on ascorbic acid who thought they were on placebo!

The success of the placebo is directly proportional to the quality of doctor-patient relationship, the doctor's attitude towards the patient, his ability to convince the patient that he is not being taken lightly, and his success in gaining full confidence of the patient. A striking example of a doctor's role in making the placebo work is seen in a study in which patients with bleeding peptic ulcers were divided into two groups. Members of the first group were informed by their doctor that a new drug had just been developed that would undoubtedly provide relief. The second group was told by nurses that a new experimental drug would be administered but that very little was known about its

effects. 70% of the patients in the first group received sufficient relief from their symptoms. Only 25% of the patients in the second group experienced similar relief. Both groups had been given an identical drug – a placebo!

Dr. Henry Beecher, noted anaesthesiologist at Harvard, in Boston, USA, compiled the results of 15 studies involving 1082 patients. 35% of patients consistently experienced satisfactory relief when placebos were used instead of regular medication for a wide range of medical problems including severe post-operative wound pain, sea sickness, headache, anxiety and coughs. Other conditions responding to placebos were rheumatoid and degenerative arthritis, peptic ulcer, hypertension, hay fever, Parkinsonian tremors, mental depression and warts.

The pattern of the response to placebo typically resembles the pharmacologic findings of active drug responses. Placebo response is not limited to the patient's subjective experience, placebos alter laboratory values and other measures of objective physiologic change. In one study of the effect of both clofibrate and placebo on cholesterol level and cardiovascular mortality, those control subjects who reliably took their placebos showed lower cholesterol and reduced mortality compared with their less compliant counterparts.

Placebos can also cause many of the same side-effects seen with active medication. For instance, when a group of patients were given a placebo in place of an anti-histaminic drug, 77.4% reported drowsiness which is characteristic of the anti-histaminic drugs. This shows the influence of the *patient's expectation from the prescription.*

The placebo, then, is not so much a pill as *a process;* the process begins with the patient's trust and confidence in his doctor and extends through to the full functioning of his own neuro-endocrine and immunological and healing capacity. The placebo does not fool the body, it translates the *will to live* and *to get well* into a physical reality. In this sense, the doctor is himself the most powerful placebo. The placebo effect pervades much of medical practice even when no placebo has been used. For example, when meprobamate, phenobarbitone and placebo were administered blindly to anxious patients, the two pharmacologically active drugs were clearly superior to placebo when administered by a physician who had confidence in the drug's efficacy and who was viewed by the subjects as supportive; the drugs and placebo showed no difference when administered by a less supportive and more skeptical physician. Subjects of the first physician also showed more overall symptom

relief. It is reasonable to suspect then, that when a family physician prescribes decongestants for a viral upper respiratory infection, some of the patient's symptom relief is due to the pharmacological action of the drug, but some is also due to the emotional support of the doctor-patient relationship, the doctor's confirmation and legitimization of the illness, and the reassurance that the symptoms do not represent something more serious than a bad cold.

As Shapiro has pointed out, a placebo is any treatment or aspect of treatment that does not have a *specific pharmacologic action* on the patient's symptoms or disease. Thus the definition of a placebo is not limited to inactive substances used for controlled clinical trials but also includes various non-specific aspects of therapy, such as the therapeutic setting. This applies to "nature cure clinics" or "hotsprings".

Human beings are highly suggestible. Expectations from the treatment being given can change people's attitudes, their moods and feelings, and can even make them believe they have experienced events that never in fact occurred.

Study of the placebo effect has clearly shown that not only can positive therapeutic effects be achieved by suggestion, but negative side-effects and complications can similarly result. Explicit suggestions of possible beneficial (or adverse) effects cause subjects to experience these effects. I am sure, once this realisation is brought home to the students and practitioners of Ayurveda and Homoeopathy, and once they imbibe the objectivity that is the essence of the scientific attitude, their own approach to their science and practice of medicine will change.

The three recognized components of the placebo effect, the physician-patient relationship, the beliefs and expectations of the patient, and the beliefs and expectations of the physician, are all used effectively in maximising the benefits obtained from any therapeutic encounter. As the doctor-patient relationship is rediscovered as a worthy focus for medical education and research, it also poses a formidable obstacle in evaluating the pharmacological action of drugs, ancient or modern. As an illustrative example, we may consider drugs used in a common and important condition, angina pectoris due to ischaemic coronary heart disease.

Angina Pectoris and the Placebo Effect

Many types of therapy for angina pectoris have been advocated, only to be abandoned later. A partial list would include heart muscle extract,

pancreatic extract, various hormones, X-irradiation, anticoagulants, monoamine oxidase inhibitors, thyroidectomy, radioiodine, sympathectomy, various vitamins, choline, meprobamate, ligation of internal mammary artery, epicardial abrasions and cobra venom. Few carefully controlled trials of these approaches were performed before the 1960's. *Failure to rule out experimenter bias* renders these investigations incapable of providing accurate evaluation of the procedure. However, this very weakness provides an opportunity to quantify the degree to which the placebo effect may have operated. Since we now know that most of these earlier forms of therapy have no specific effect in the treatment of angina pectoris, we can analyze the benefits reported and assess the degree of influence of the placebo effect.

There is general *enthusiasm* when a new drug or a new form of therapy is introduced for the first time, and *hope* for its effectiveness. The *enthusiasts* report remarkable benefits in the vast majority of patients. The placebo effect is operating maximally under these circumstances. Later when skeptical investigators try out the same therapy, they are operating under circumstances that minimize the placebo effect, and find the therapy "no better than" inert control placebo pills.

Quantitatively the pattern is consistent. The initial 70 to 90 per cent effectiveness in the enthusiast's reports decreases to *30 to 40 per cent* * *"baseline" placebo effectiveness* in the Skeptic's report. This pattern was recognized by the 19th century French physician Armand Trousseau who stated "you should treat as many patients as possible with the new drug while they still have the power to heal".

In a controlled trial, effort is made to *quantify objectively* a drug's effectiveness, for example exercise tolerance. However, even exercise tolerance is subject to the placebo effect.

It is important to realise the placebo effects of surgery. For instance, controlled studies have demonstrated that a mere skin incision could lead to a dramatic, sustained placebo effect comparable to actual surgical procedure like ligation of the internal mammary, or implantation of the internal mammary artery. It is important to note that in none of these controlled studies did improvement correlate with angiographic evidence of revascularization. It is food for thought that 10,000 to 15,000 such operations were performed with an average

* Beecher, in his review of 15 trials that involved 1082 patients with a wide variety of ailments found a baseline placebo effectiveness rate of $35.2 \pm 2.2\%$ (Mean $\pm$ SD).

operative mortality of approximately 5 per cent, before the procedures were abandoned as of no benefit.

Duration of Placebo Effect

Although the placebo effect is commonly believed to be of limited duration, many reports indicate relief for a year or more; the placebo effect will most likely persist as long as the psychologic context in which it was evoked remains unchanged. Patient and physician belief in the efficacy of the therapy and a continuously strong physician-patient relationship will maintain the placebo effect for long periods. Conversely, a poor physician-patient relationship, or patient's doubt or physician's doubt about the therapy would quickly abolish the placebo effect.

The degree of placebo effect in relief of angina pectoris may differ as a function of the degree of coronary artery disease present. Even in patients with angiographically verified coronary-artery disease, substantial placebo-effect relief occurred in 60 to 80 per cent of patients with the Vineberg procedure (implantation of internal mammary artery) which as we now know did not really increase the blood flow to the myocardium.

Recently treatments with proved specific physiologic efficacy in angina patients, such as beta-blockers have been developed. The very *expectation of good results* acts synergistically with the active therapy to bring about those results.

The advent of a ''new'' procedure may impair the effectiveness of an ''old'' one. The expectations of better results transfer the placebo effect to the new procedure, even though, for at least 40 years the new treatments have been no more effective than the old, when these old treatments were new.

The role of endorphins in placebo-effect in pain relief needs further study.

In a variety of painful conditions a remarkably constant proportion (about one-third) of patients obtain significant relief from a placebo. Endogenous opiates (endorphins) seem to be involved in this pain relief since naloxone, a specific morphine antagonist, causes a significantly greater increase in pain ratings in placebo-responders than in non-responders. Furthermore, prior administration of naloxone reduces the probability of a positive placebo response. Hence, the placebo effect

may be mediated by endorphins. Recently an endogenous pain-suppressor system has been described, which can be activated by electrical stimulation of the brain or by systemically administered opiates. Conceivably, the analgesic effect of placebo upon clinical pain results from activation of the same pain-suppression system. Greater understanding of endogenous mechanism of analgesia should lead to more effective management of clinical pain with a combination of pharmacological and physical methods.

Problems in Evaluation of Drugs

Since the placebo effect has always been the physician's most potent therapeutic asset, it has always been possible to achieve marked symptomatic improvement even with inactive substances or ineffective procedures, in about 80 per cent of patients safely and inexpensively. Herein lies the problem of scientific evaluation of Ayurvedic, Homoeopathic or any other drugs, ancient or modern. In a successful therapeutic encounter, how much credit can be given to the pharmacological activity of the drug and how much to the other factors? Such questions vexed the ancient Indian physicians as well, as is evident from the following discussion in *Charaka Samhita.*

While discussing the fourfold basic factors in therapeutics, Maitreya makes a proposition: "There are seen some patients possessed of means, having attendants, self-controlled and treated by expert physicians, recovering, while some others though enjoying similar amenities, dying nevertheless. Thus, treatment becomes a thing of no consequence."

"Conversely we see others, devoid of means, with no attendants, no self-control, and treated by unskilled physicians, regaining health; and yet others, similarly circumstanced, dying all the same."

"Thus, recovery follows treatment, death too follows treatment. Similarly recovery follows in the absence of treatment, and in the absence of treatment, death too follows. Hence, it is to be concluded that treatment is in no way better than no treatment".

In Maitreya's proposition, we see two concepts of relevance today. One is the *variable natural history of diseases* and second is the *Null Hypothesis* (that treatment is in no way better or different than no treatment) used in modern statistical theory.

Atreya's reply to this null hypothesis is: "Just as a man, by lifting another who has fallen although the latter is able to rise by himself,

gives him support in consequence of which he rises sooner and without difficulty, in like manner do patients receiving the aid of a complete treatment, recover more easily and without difficulty''.

Atreya was *comparing* a treated group and a non-treated group and claiming that the treated group *recovered more easily* than the un-treated group, thereby *rejecting the Null Hypothesis.*

Claude Bernard (1813-1877), father of the Experimental Method in medicine, wrote in 1864—''We cannot judge the influence of a remedy on the course and outcome of a disease if we do not previously know the natural course and outcome of the disease. To be valid, comparative experiments have to be made at the same time and on as comparable patients as possible. Inspite of that, such comparisons still bristle with immense difficulties which physicians must strive to lessen. For comparative experiment is the *sine qua non* of scientific experimental medicine. Without it, a physician walks at random and becomes the plaything of endless illusions. A physician who tries a remedy and cures his patient is inclined to believe that the cure is due to his treatment. Physicians often pride themselves on curing all their patients with a remedy that they use. But the first thing to ask them is whether they have tried doing nothing i.e., not treating their patients, for how can they otherwise know whether the remedy or nature cured them? Comparative experiment has shown in fact that treatment of pneumonia by bleeding, which was believed to be most efficacious, is a mere therapeutic illusion''.

Therapeutics is an Experiment

Sir George Pickering wrote in 1949: ''Therapeutics is the branch of medicine that, by its very nature, should be considered as experimental. For, if we take a patient afflicted with a malady and we alter his condition of life, we are performing an experiment. And if we are scientifically minded we should record the results. Before concluding that the change for the better or for worse in the patient is due to the specific treatment employed, we must ascertain whether the result was merely due to the *natural history* of the disease or whether it was due to some other factor which was *necessarily associated* with the therapeutic measure in question. And if, as a result of these procedures, we learn that the therapeutic measure employed produces a significant though not very pronounced improvement, we would experiment with the method, altering dosage or other detail to see if it can be improved.''

Dr. Alvan R. Feinstein in 1967 compared the therapeutic experiments that clinicians constantly perform, to the laboratory experiments performed by basic scientists. "Every aspect of clinical management can be designed, executed and appraised with intellectual procedures identical to those used in any experimental situation".

There are some who dislike or reject the notion of deliberate experimentation on the sick, feeling that a scientific approach implies an unsympathetic or even a malevolent disposition. They conveniently forget that throughout the history of medicine, many useless therapies and many positively harmful therapies (like blood-letting in pneumonia) have been practised, though with the best of intentions, because of the *lack of recognition of the need as well as the lack of knowledge of the techniques, of scientific evaluation of therapy.* Where the worth of a treatment, new or old, is in doubt, there may be a greater obligation to test it critically than to go on prescribing it, supported merely by habit or wishful thinking.

The choice before the doctor is not whether he should experiment on his patient, but whether he should do so in a *planned* or in a *haphazard* fashion. To rely on unsubstantiated impressions is the less ethical course to follow than planned experiment. Anyone who thinks he can assess the value of any but the most dramatically effective treatments by using them on patients in an uncontrolled fashion has the whole history of therapeutics against him.

Modern scientific techniques can uncover the most effective treatment exposing the smallest numbers to those that are less effective or even positively harmful. They save lives, time and money.

Need for Statistical Methods

In order to decide whether patients treated in one way are benefitted more than those treated in another, there is no possibility of avoiding the use of numbers. Convincing facts are better than opinions. This is not to dismiss the anecdotal survey or the case report, for they tell what can happen, which is useful.

As a pioneer in clinical statistics in 1835 Pierre C. A. Louis (1787-1872) published an account of 77 patients of pneumonia. He counted and compared the results of patients treated by blood-letting, and showed that early bleeding was associated with *reduced* survival. He concluded his treatise on blood-letting with these comments: "Let those who engage hereafter in the study of therapeutics pursue an opposite course to that of their predecessors. Let them not think that

they have done anything effectual, when they have only displayed their own theories, or stated what is done by the most-celebrated physicians in such and such a case. But let them labour to demonstrate rigorously the influence, and the degree of influence of any therapeutic agent, on the duration, progress and termination of a particular disease''.

Louis' numerical method was a rational instrument to help the mind. What he did was to initiate the concept of clinical statistics, and point out the fallacy of *"pôst hoc ergo propter hoc"* theory: The clinician gives a particular therapy; the patient gets better; the clinician concludes that *because* he gave the treatment, *therefore* the patient got better. This may or may not be true. In the specious self-deception of the ''post hoc'' clinical reasoning many a drug, diet or device of ancient and modern medicine has been given false credit for the patients' improvement that was due to nature or to man himself.

The pioneering work of Louis helped end the popularity of blood-letting, but it is not cited in most contemporary books on epidemiology or biostatistics.

A century ago, Francis Galton (1822-1911) said this: ''In our general impressions far too great a weight is attached to what is marvellous. Experience warns us against it, and the scientific man takes care to base his conclusions upon actual numbers. The human mind is a most imperfect apparatus for the elaboration of general ideas. General impressions are never to be trusted. Unfortunately, when they are of long standing they become fixed rules of life, and assume a prescriptive right not to be questioned. Consequently, those who are not accustomed to original enquiry entertain a hatred and a horror of statistics. They cannot endure the idea of submitting their sacred impressions to cold-blooded verification. But it is the triumph of scientific men to rise superior to such superstitions, to devise tests by which the value of beliefs may be ascertained, and to feel sufficiently masters of themselves to discard contemptuously whatever may be found untrue. The frequent incorrectness of notions derived from general impressions may be assumed''.

Statistics tell us of probabilities. Reasonable certainty is only obtained when there are several independent studies all reaching similar conclusions. Absolute certainty is only attained where there is certain knowledge of mechanisms so that statistics become unnecessary.

Aims of a Controlled Therapeutic Trial

With controlled therapeutic trials we attempt to determine:

1. whether a treatment is of value,
2. how great its value is compared to other remedies if such exist,
3. in what types of patients it is of value,
4. what is the best method of applying the treatment; if it is a drug, what dosage and frequency,
5. what are the disadvantages and dangers of the treatment.

All these aims can be achieved by randomized control trial carefully planned, executed and analysed with the help of statistical techniques.

Sir Austin Bradford Hill, the doyen of medical statisticians, defined the therapeutic trial as "a carefully and ethically designed experiment with the aim of answering some *precisely framed question.* In its most rigorous form it demands *equivalent groups* of patients *concurrently treated in different ways.* These groups are constructed by the *random allocation* of patients to one or the other treatment. In principle the method is applicable with any disease and any treatment. It may also be applied on any scale; it does not necessarily demand large numbers of patients".

A sound guide to ethical conduct of a trial is that no patient should be worse off as a result of a drug trial than he might have been otherwise in the hands of a reasonable and competent medical man. If it is not known whether one treatment is better than another, then nothing is lost by allotting patients at random to those treatments under test and it is in everybody's interest that good therapies should be adopted and bad or useless therapies abandoned as soon as possible.

For example, suppose we have a number of children all of whom have been in contact with measles and to a proportion of them is given an injection of gamma globulin. We wish to know whether the treatment prevents the development of a clinical attack. It is possible that the risk of developing an attack is influenced by age, by sex, by social class (and all that it denotes), by duration and intimacy of contact, by general state of health. A statistical analysis necessitates attention to *all* these possible influences. We must endeavour to equalise the groups we compare in every possible influential respect except in the one factor at issue—namely, the treatment. If we have been unable to equalise the groups initially, we must equalise them to the utmost extent by the mode of analysis. It is clear that as far as possible we should endeavour to eliminate, or allow for, these extraneous or disturbing causes when the observations are planned. With such planning, may be we can determine not only whether the treatment is of value but whether it is more effective at one age than another.

Elaborate experiments can be planned in which quite a number of factors can be taken into account statistically at the same time. The essence of the problem is to ensure before hand in a therapeutic trial, that the *control* and *treated* groups are *similar* in all *relevant* respects. The onus of knowing what is likely to be relevant in a specific problem must rest upon the experimenter. The important point is *taking care of all variables* in planning the experiment and in analysing the results.

In interpreting the results in the above-mentioned example, suppose we find that Group A (given the gamma globulin injection) differs from Group B (control) in some characteristic, say, its mortality rate, can we be certain that, the difference is due to the fact that Group A was given gamma globulin and Group B was not? Are we certain that Group A did not differ from Group B in some other character relevant to the issue as well as in the presence or absence of inoculation? For instance the treated group might belong to a higher social class than the untreated, and therefore live in surroundings in which the risk of infection was less. We can never be certain that we have not overcome some relevant factor or that some factor is not present which could not be foreseen or identified. It is because he knows a complex chain of causation is so often involved, that the statistician is apparently an unduly cautious and sceptical individual. But in the pursuit of scientific facts, caution and scepticism are important virtues while gullibility is not. Uncritical acceptance of unsubstantiated claims has allowed thousands of useless remedies to be used throughout the history of medicine, and without critical controlled trial the same trend may continue in future.

The essence of a therapeutic experiment in the treatment of a disease lies in *comparison*. All science is measurement, and all true measurement is essentially comparative. Many people argue that human beings are too variable to allow of the contrasts inherent in a controlled trial of a remedy. Yet if each patient is "unique" it is difficult to see how any basis for treatment can be sought in the past observations on other patients—upon which clinical medicine is founded In fact the physician's treatment of choice is based upon what he has seen (or read) happen before—whether it be in only two or three cases or in a hundred. Therefore, far from arguing that the statistical approach is impossible in the face of human variability, we must realise that it is *because* of the variability that statistical approach is so very essential.

How large a number of observations do we need in establishing the superiority of one treatment over no treatment or another treatment?

It depends upon the problem. If for example, we were to try a new drug in a proved case of acute leukemia and the patient made an immediate and indisputable recovery, we should have a result of the most profound importance. Our acceptance of a remarkable event of merely one patient—not necessarily cause and effect—is based on previous experience that in their response to acute leukemia human beings are *not variable*. They all fail to make immediate and undisputed recoveries, and they all die. Therefore, it would be sheer madness not to accept the evidence presented by one case, although we would then proceed to apply the other scientific criterion of *reproducibility* by using the remedy on other similar patients.

If on the other hand the drug was given to a patient suffering from acute rheumatic fever and the patient made an immediate and undisputed recovery, we have little basis for remark, because with this disease human beings *are variable* in their natural course; some make immediate and undisputed recoveries even without any treatment, some may have prolonged illness but recover eventually with or without permanent damage, and some may die. We must therefore have more cases before we can reasonably draw inferences about cause and effect. We need a statistical approach and a designed experiment.

One difficulty, in view of the variability of patients and their illnesses, is in *classification* of the patients, at least in broad groups, so that we may be sure that like is put with like, both before and after treatment. We must be particularly careful that in making broad groupings, we sacrifice nothing relevant to the issue, or more than is essential to clarity and ease in handling, interpreting and presenting data on large number of patients. Feinstein introduced in the 1960's the idea of classifying different *clinical subgroups* that constitute the diverse spectrum of a human disease, by depicting them as Venn diagrams. Boolean algebra and Venn diagrams are a perfectly intellectual mechanism for classifying overlap; they are an ideal way to distinguish multiple properties that could be present or absent, alone or in combination. On the basis of clinical experience and ordinary clinical logic Feinstein has shown the prognostic clinical spectrum of patients with bronchogenic carcinoma. Of the eight subsets of patients all under the heading of "bronchogenic carcinoma", prognostic anticipation can be made in different subsets, which take into account primary and systemic symptoms and their duration, local and metastatic spread, weight-loss. Although the total 5-year survival was 9% for the entire population of 596 cancer patients, the rates ranged from 32% in stage

I, 18% in stage II, 10% in stage III, 8% in IV and 0.6% in V. The importance of such classification which takes into account not only morphology but also symptomatology and its temporal profile, is important in planning and evaluating therapeutic trials. The same applies to the clinical spectrum of ischaemic heart disease with different prognostic clusters, which must be taken into account while evaluating various modes of therapy.

Importance of Randomization

Clinicians try their treatment on a series of patients and analyse and publish their results. The point worth appreciating is that studies on a series of cases, while advancing correct understanding, can promote the pursuit of bad leads as well. Nearly every discarded, once popular therapy was probably supported at one time by a series of favourable cases! The strengths and weaknesses of series as information sources, deserve analysis. A series is a study of the outcome of an intervention applied to all eligible subjects, chosen by criteria that depend only on pre-treatment status.

A number of factors bear upon the interpretation of a report of a series. *Selection* can grossly affect the data. Without complete *follow-up* the available figures lose much of their meaning. Adjustment has to be made for interfering variables. *Who* were the subjects? *What* was done? *By whom* was it done? *When* was it done? *Why* was it done? All these should be clearly stated.

The randomized clinical trial is especially effective in taking care of variables, especially the problem of sub-groups within large groups. One has also to consider the *temporal drift* if the series has accumulated over a long period of time.

Statistical inference is a powerful tool for learning from experience, if data is obtained with *random sampling* from a population, or with data from a *randomized* Clinical trial. "Grab samples" can lead to treacherous conclusions. It is not impossible to reach valid conclusion from grab samples, but the process is fraught with difficulty, uncertainty and error except in cases where the results of therapy are dramatic and spectacular, like ether in anaesthesia, penicillin in syphilis and subacute bacterial endocarditis, vitamin B12 in pernicious anaemia, cortisone in adrenal insufficiency, methotrexate in choriocarcinoma and propranolol in hypertrophic subaortic stenosis. Unfortunately in most other situations the results are not as clear-cut, hence the need for a large sample in a randomized clinical trial.

To my mind the most important landmark in the development of the scientific practice of medicine in the 20th century is the intellectual approach to therapy as a planned scientific experiment. The experiments at the bedside and laboratory differ fundamentally not in their basic intellectual construction, but in their materials and modes of inception. Both types of experiments need a plan, a method of execution of the plan and an appraisal of the results. In clinical treatment the main motives of the therapeutic experiment are remedial and prophylactic, to change what Nature has done, or to prevent what it may do.

It is my earnest hope that students and practitioners of Ayurveda and Homoeopathy will assimilate the ideas about scientific evaluation of therapy, propounded so far, in their own thinking. It will drastically change their entire approach to their therapy. They will themselves then be in a position to ascertain the "placebo effect" as opposed to the pharmacological effect of their therapy.

A Rational Approach for Investigation of Traditional Therapeutics

In the past, the standard approach by Western-trained medical scientists and pharmacologists to traditional Ayurvedic medicines has been: (1) to select a plant or remedy based on the study of literature or experience of practitioners of traditional medicine, (2) to get it identified, (3) to make various aqueous, alcoholic, ether, petroleum etc. extracts, (4) to determine LD 50 by oral and intraperitoneal route on two or three species of animals, (5) to do general pharmacologic tests on animals at 1/5 and 1/10 LD 50, (6) to study it in mice, rats, guineapigs or rabbits for different effects. For instance the study of drugs for fertility control would include: (a) anti-implantation studies (b) resorption of fetus (c) litter size (d) fetus study for abnormalities (e) study effect of feeding on days of organogenesis (f) feed during entire pregnancy and study effects (g) study effects on second and third generations etc. Then chemistry studies would be started to isolate fractions and attempt to determine active principles. All the studies would then be repeated with isolated chemical molecules to find out what is active. Then toxicity studies would be undertaken which would normally last two years in rats and 6-12 months in dogs. Mutagenic studies and effects on chromosomes would be studied. Even after starting clinical trials, toxicity studies would continue in dogs or monkeys for the next seven years (as required in U.S.A. by Food and Drug Administration).

Clinically phase I studies for safety, effects on hormonal pattern, cervical mucous studies and endometrial biopsy studies would be done. Thereafter phase II and III studies would begin. All this would take 7-10 years and a full team of scientists and investigators, costing several crores of rupees.

This obviously too expensive and time-consuming approach which has been used for synthetic drug development in the West is not suitable for application to the investigation of traditional medicines. Certain reasons permit a different approach. To list them:

1. The traditional drugs have been in use for hundreds of years and obviously a toxic drug could not have stayed on the scene for such long periods.
2. The patients are willing to take traditional drugs from their Vaidyas in any case, whether or not a controlled clinical trial is held, hence the question of ethics will not arise.
3. The safety and efficacy of traditional drugs can be studied in these patients, without disturbing their routine treatment, by applying modern investigatory parameters.

Drugs in Ayurveda are prepared in a particular way. Very often the method of preparation alters the chemical structure, bioavailability etc., of the original plant. Theoretically at least, other methods of preparing plant extracts may lead to a loss of activity or increase in toxicity. This has been the painful experience for many pharmacologists. Keeping all these factors in mind, the traditional vaidya should give the medication as per his method and the modern investigator should watch the results as an unbiased observer, using modern scientific parameters of measuring effectiveness and safety.

In collaboration with Ayurvedic physicians correct recording protocols should be drawn out. Such an approach is likely to produce a meaningful answer in 1—2 years with a limited budget. If any remedy proves safe and effective, then it could be the starting point for further research. Examples of such research are given in Chapter 16, Pharmacology Ancient and Modern.

Unnecessary Medication—Who is to Blame?

Richard Cabot wrote at the beginning of this Century: "The majority of placebos are given because we believe that the patient will not be satisfied without them. He has learned to expect medicine for every symptom and without it he simply will not get well. True, but who

taught him to expect a medicine for every symptom? He was not born with that expectation. He learned it from an ignorant doctor who really believed it. It is we physicians who are responsible for perpetuating false ideas about disease and its cure, and with every placebo that we give we do our part in perpetuating error, and harmful error at that."

It has been said that the use of placebos is in inverse ratio to the combined intelligence of patient and doctor. It is my belief that the medical profession has not fulfilled its function as advisers and educators of the patients. It is my personal experience that a patient who has come to me with faith in my competence and judgement will not be disappointed if I do not give him any pills, as long as I help him and guide him in the solution of his problems. Very often the advice is related to change of health-related behaviour—regular physical exercise, weight reduction, giving up smoking or excessive drinking, avoidance of tensions and learning to relax etc. An insistent demand for a "tonic" can be met with persistent advice that a balanced diet is the best tonic. The medical profession seems to be trapped in a vicious circle in which, as the argument goes, "If I do not give the pill or the injection as expected by the patient he will go to another doctor who will give it and I will lose the patient". Such a position is similar to that claimed by the Indian film producer who "has to insert scenes of rape, violence and sex to succeed at the box office, since the public ask for it." I do not subscribe to this way of thinking. Once clinicians realise the extent to which simple information and encouragement can elicit a positive response, the perceived need to use placebo will be markedly diminished.

Attraction of Alternative Approaches

Currently there is great public interest all over the world in alternatives to modern medicine. Partly at least, it stems from dissatisfaction with the medical service or the doctors. Inaccessibility of doctors, poor communication between doctors and patients, preoccupation with high technology, excessive prescribing and high cost of treatment, are criticisms which are at times and in some situations and circumstances true.

Ever since the danger of thalidomide given to pregnant women was discovered, people have become aware that modern drugs are not to be regarded solely in a life-saving role; they can be powerfully dangerous, even when taken as directed by the physician. With the widespread use of antibiotics, pain-killers, corticosteroids and the non-steroid anti-inflammatory drugs, the public awareness of the potential dangers of

modern drugs rose very sharply. The result was a growing distrust not just of the highly sophisticated new drugs, but of almost all modern medicine in general. People became attracted more and more towards alternative modalities because of their "safety." It is easy enough to concede the *safety* of many therapies; the same cannot be said about their *efficacy.* I am absolutely certain that if the practitioners of Ayurveda, Homoeopathy and other methods of therapy scrutinise their therapy with the same scientific rigour as applied recently by modern medicine, they will discover that *much of what they do is placebo therapy.* Public fear about modern medicine should be an opportunity for better health education rather than replacement of effective but risky therapy by safe but ineffective therapy. Intellectual honesty is required for any self-scrutiny.

Do People Really Want Science?

The story of Laetrile is worth telling in detail, in view of its implications for understanding public attitudes to science.

Amygdalin (Laetrile) has had many centuries of use for medical purposes, perhaps first documented by Dioscorides shortly after the birth of Christ. Usually administered in the form of bitter almonds, it was a common ingredient of herbal prescriptions for a variety of illnesses, and by a liberal interpretation of ancient pharmacopoeias one might conclude that it was used for the treatment of cancer. With the advent of the science of medicine, amygdalin, along with most other herbal agents, was abandoned for clinical therapy. In 1952, however, it was revived by Ernest Krebs Jr. who registered it with the United States Post Office under the trade name of *Laetrile,* to be used for the treatment of "disorders from intestinal fermentation"—i.e. cancer. Laetrile therapy made claims of effectiveness in patients of advanced cancer in whom standard treatment had failed.

In the United States the Food & Drug Administration (FDA) requires evidence of *safety* as well as *efficacy* before permitting use of a drug. Due to lack of any evidence of efficacy in animal models of cancer (which have helped in the evaluation of several other effective anti-cancer drugs), the FDA decided to ban the drug. Furthermore, commercial preparations imported from Mexico, tested in the U.S. National Cancer Institute, were found to be chemically subpotent, microbiologically contaminated and unfit as pharmaceutical products for human use. Virtually every reputable cancer specialist and major medical organization in U.S.A. opposed the introduction of Laetrile.

Yet Laetrile was pushed by enthusiastic supporters as a cancer cure. The American public perhaps thought that the "medical establishment" was stubbornly overlooking a valuable adjunct in cancer therapy. By 1978 Laetrile had achieved a certain folk status, celebrated as a kind of anti-establishment natural remedy being suppressed by a venal conspiracy between U.S. physicians and the drug industry. According to public opinion the medical conspirators were ignoring evidence of Laetrile's effectiveness and attempting to promote their own orthodox (and more toxic) forms of cancer chemotherapy. A nation-wide Harris poll showed that the American public favoured legislation to legalize Laetrile by an amazing 30 per cent margin. The drug has been legalized in 27 out of 50 states in U.S.A. and a Federal Court has forced the FDA to allow its legal nationwide use.

In 1982 a prospective clinical trial on 179 patients of a variety of types of well-documented cancer was undertaken by the National Cancer Institute (NCI) in U.S.A. The pharmaceutical preparations of amygdalin, the dosage, and the schedule were representative of past and present Laetrile practice. *No substantive benefit was observed* in terms of cure, improvement of symptoms related to cancer, or extension of life span. *The hazards* of amygdalin were evidenced in several patients by symptoms of *Cyanide toxicity* or by blood cyanide levels approaching the lethal range. The conclusion was that Laetrile was a toxic drug and that it is not effective as a cancer treatment. Laetrile has been advertised to the public, the state legislatures and the Courts as a non-toxic drug. The evidence for the lack of toxicity was no better than the evidence of its favourable therapeutic effects. It remains to be seen if the NCI-controlled clinical trial of 1982 changes the attitude of the Courts and the public and the mass media. The basic issue here is not one of proving once and for all that Laetrile is worthless in the treatment of cancer, because there will be yet another claim from yet another source. The issue is an emotional one, not a scientific one. When people are faced with incurable and fatal diseases, any one who can sell "hope" can capture people's minds; the source of that "hope" may be honest physicians, Godmen or priests, or charlatans and unscrupulous rogues. Disillusionment comes in course of time, but another generation of hopefuls will replace the disillusioned, hence the process continues.

It is reasonable to expect the modern physician to maintain an open mind about claims in treatment even though they may not be in harmony with his own training and experience. But it is not reasonable to

expect him to proceed with any alternative mode of treatment in the absence of adequate evidence that it is safe and effective. Research and clinical evaluation of alternative methods is urgently needed to avoid both missed opportunities and false hopes.

It is reasonable to expect the modern physician to recognize that science may not have all the answers to problems of health and healing. But it is not reasonable to expect him to give up the scientific method in treating his patients. The most important thing about science is the scientific method—a way of thinking systematically, a way of assembling evidence and appraising it, a way of conducting experiments so as to predict what would happen under given circumstances, a way of ascertaining and recognizing one's own errors, a way of finding fallacies in long-held ideas. Science is itself constantly changing, largely as a result of the scientific method.

Chapter 4

CLASSIFICATION
ANCIENT & MODERN

Introduction

Classification is defined as the ordering or arrangement of objects into groups or sets on the basis of their relationships. These relationships can be based on *observed* or *inferred* properties. Once classes are established, the allocation or assignment of unidentified objects to the correct class is "identification". Some philosophers, statisticians and mathematicians also employ the term classification for what is here called identification.

The term taxonomy (Greek *taxis* for arrangement or order, *nomos* for law) is used to indicate the theoretical study of classification, including its bases, principles, procedures and rules. This would include classification as well as identification. It is the science of 'how to classify and identify'.

The origin of the science of classification is generally traced back to the writings of ancient Greeks, not realising the tremendous contributions made by ancient Indians. The one thing that impressed me most during my study of Ayurveda is the tremendous flair of the ancient Indian Masters for classification, and their vast array of nomenclature.

Nomenclature is the naming of objects (in the context of medicine, naming of morbid conditions). Ayurveda has extensive nomenclature which covers many anatomical, pathological, clinical and therapeutic areas. The concepts of classification and nomenclature are closely related; the element of *grouping* distinguishes classification from nomenclature.

Classification is an important aspect of most sciences, and the subject of classification in Medicine continues to engage the minds of many thinking people. How *do* we classify and how *should* we classify? Classification is based on the recognition of similarities. What is similarity? How do human beings recognize similarity?

Impact of Computers on Taxonomy

The interface with the modern computer has forced clinicians to re-examine more critically their concepts of classification. Computers play a central role in modern classification for four reasons. Firstly they have helped to find solution to problems that were analytically intractable. Secondly, computers are able to carry out computations whose numerical solutions were known but exceedingly tedious. Also computers have been able to classify simultaneously for larger numbers of objects, using many more features of these objects, than any human taxonomists. Thirdly, algorithms of computer classification have led to *objectivise* and *optimise* the classification process. Fourthly, because of the general development of pattern recognition and perceptron technology, the availability of computers has given rise to fundamental investigations into how human beings perceive the world around them. In contemporary science, taxonomy has become an important creative intellectual discipline. If it is the purpose of science to discover the true nature of things then a classification should describe objects in such a way that their true relationships are displayed.

Disease classification—Nosology

As physicians we observe phenomena in the patient (symptoms and signs) and we develop ideas and theories to account for these observations. Hippocrates is given the credit for bringing medical observations alongside the observations of other natural phenomena such as the stars in astronomy. He states: "It is the business of the physician to know in the first place, things most important, most easily known, which are to be perceived by the sight, touch, hearing, smell and taste, and the understanding; things which are to be known by all the means by which we know all other things." Identical approach has been emphasised by Charaka and Sushruta.

In the ancient nosology, there were two steps in the classification process – *the observational* or *empiric approach,* the classified entity being a phenomenon that has actually been *witnessed.* An important intellectual step following observation is the process of *induction* to make *generalizations.* In the words of Hippocrates: "What escapes the eye is mastered by the eye of the mind; the attendant tries to track it by reasoning. Some symptoms indicate that a part is affected; others that a part may be affected thereafter. When this information is not afforded and Nature will yield nothing of her own accord, medicine has found methods of compelling Nature to give up her secrets".

In the *inferential* or *hypothetical approach*, the classified entity is a *deduction* or *speculation about the cause*. The Ayurvedic hypothesis of causation was based on *"Tridosha" – Vata, Pitta & Kapha*. It is important to make a distinction between *observed facts* (about which there can be no disagreement) and *concepts of their causation* (about which there can be genuine disagreement). Idealised conceptual classifications often relate to examination of an underlying hypothesis such as the concept of phylogeny implicit in botanical and zoological taxonomies. Problems in medicine are at once more changeable and immediate, and they relate to *processes* rather than to objects. Knowledge in medicine has not yet reached a stage that would permit development of so comprehensive a theoretical framework. The main thrust of the various chapters in this book is to indicate how far we have come from ancient *speculative concepts* like the *"Tridosha"*, to the modern concepts based on *observations* and *experimental verification*. Today we have a much better understanding of causation of symptoms and signs and their underlying pathophysiology and their causative factors (etiology), than ever before.

Various Objectives of Classification of Diseases

It is axiomatic that classification is subordinate to a purpose. Thus to evaluate a classification one need consider its conformity to only a single criterion – that of *utility*. Does the taxonomy do what you want it to do? Any attempt to develop a classification should commence with a clear statement of its purpose. There are two main contexts in which the physician constructs conceptual taxonomies. First, he would need a scheme to interrelate biomedical phenomena in such a way as to enhance his *understanding* and to suggest avenues for further study and research. Secondly *clinical decision-making* will call for a rather simpler therapeutic scheme which will indicate, for instance, in the context of rheumatoid arthritis, that this is an "aspirin" patient and that is a "penicillamine" patient. Similarly in the context of fever, this is an "antibiotic" patient and that is an "aspirin" patient.

Take for instance this *binary* classification of Charaka: "Diseases are divided into two groups on the score of their *effects:* curable and incurable; on the score of their *intensity;* mild or severe; according to the *seat of affection:* mind or body; according to their *cause:* endogenous or exogenous".

For public health purposes and health service planning a more practically oriented classification like *causes of death* will suffice. William

Farr (1807 – 1883) made the best possible use of the imperfect classification of diseases available in England during his time and utilised information by arranging it in five groups – epidemic diseases, constitutional (general) diseases, local diseases according to anatomical site, developmental diseases and diseases that are the direct result of violence. Thus developed the statistical classification of diseases, for purposes of prevention.

The International Classification of Diseases (ICD) was developed as a means of facilitating comparability in mortality studies. The ICD is subject to decennial revision under the aegis of WHO. Previous revisions have tended to lack credibility with clinicians because the latter did not understand their limited purpose for public health measures. The 9th revision of ICD which came into use in 1979, offers options which in reality are two interdigitating but complementary classifications.

The scientific purist who will wait for medical statistics until they are nosologically exact is no wiser than Horace's rustic "waiting for the river to flow away". In selecting a classification scheme one has to make a choice, balancing gains and losses. The story of six blind men and the elephant is familiar to every one; each observer perceived elements of the whole, but perception was selective. We are similarly selective in developing concepts and in integrating them into classification schemes.

Ayurvedic Classification of Diseases

Charaka Samhita has described over 200 diseases and over 150 pathological conditions and congenital defects. I have tried to arrange them under different systems as per WHO International Classification of Diseases (ICD) – (Table I). A recent WHO Reason-For-Encounter classification is discussed subsequently.

It will be noticed from the list that many disease entities were descriptive of *topology* – the sites of trouble, such as *"Karnaroga"* (diseases of the ear), *"Ardita"* (facial palsy). Some are descriptive of *symptoms,* such as *"jvara"* (fever), *"apasmara"* (epilepsy), *"Arohavabheda"* (hemicrania). Some are descriptive of *physical appearance* – such as *"Shleepada"* (elephant leg). Many are *combinations of topology and pathology* – such as *"galaganda"* (tumour on the neck), *"Chhidrodar"* (perforation in abdomen) etc.

TABLE I

Clinical entities described in *Charaka Samhita*
Systems arranged according to WHO classification (ICD)

I Infections and Parasitic Diseases

Sannipata jvar (typhoid fever) Su, *17,* 41
Visamajvara (recurrent fever) Ci, *3,* 53
Visuchika (Cholera) Vi, *2,* 10
Visarpa (acute spreading suppuration) Ci, *21,* 29
Krmi (parasitic infections) Su, *19,* 4/9
Slipada (elephantiasis of leg) Ci, *12,* 98
Masurika (pox) Ci, *12,* 93
Kaksa (herpes) Su, *20,* 14
Dadru (ringworm) Ci, *7,* 23
Vicharchika (scabies) Ci, *7,* 26
Dhanustambha (Tetanus) Su, *20,* 14

II Neoplasms

Arbuda (non-suppurative swelling) Ci, *12,* 87
Galaganda (tumour on the side of the neck) Ci, *12, 79*
Vradhna (permanent swelling) Ci, 12, 94 5 types
Kakana (malignant growth) Ci, *7,* 20
Granthi (glandular swelling) Ci, *12,* 81
Vidardika (swelling in the groin) Ci, *12,* 79
Gulma (hard swelling) Ci, *5,* 38
Rakta granthi (tumour in bladderneck) Si, *9,* 41
Vata Sthila (hard tumour) Si, *9,* 36

III Endocrine, Metabolic, Nutritional & Immunological Disorders

Atisthula (excessive obesity) Su, *21,* 4
Madhumeha (diabetes mellitus) Ni, *4,* 44, Chi, *6,* 55-56
1. Pidaka (diabetic eruptions) Su, *17,* 82
2. Kacchapika (carbuncle single opening) Ci, *17,* 85
3. Jalini (carbuncle many openings) Ci, *17,* 86
4. Ajali (dry gangrene) Ci, *17,* 88
Shosa (wasting disease) Ni, *6,* 11
Shotha (edema) Ni, *12,* 1

IV Diseases of Blood and Blood-forming Organs

Panduroga (haemolytic jaundice) Ci, *16,* 7
Halimaka (jaundice due to anaemia) Ci, *16,* 132
Sonitakleda (pernicious anaemia) Su, *20,* 14
Srotoroga (disease of body fluids) Vi, *5,* 8 14 types

V Mental Disorders

Manovikar (mental disorders) Su, *7,* 52
Unmada (insanity) Ci, *9,* 15 types described
Durmanas (neurasthenia) Su, *17,* 73
Mada (intoxication) Su, *24,* 27 7 types

VI Nervous System and Sense Organs

Anidra (insomnia) Ci, *28,* 21
Antarayam (stiffneck) Ci, *28,* 43
Apasmar (epilepsy) Ci, *10, 3*
Apatastraka (opisthotonus) Si, *9,* 12
Arohavabheda (hemicrania) Si, *9,* 74
Ardita (facial palsy) Su, *20,* 11
Ataktyabhinivesa (psychic epilepsy) Ci, *10,* 52
Dandaka (convulsions) Su, *24,* 25
Durma (neurasthenia) Su, *17,* 73
Ekangaroga (monoplegia) Su, *20,* 11
Grdhrasi (sciatica) Su, *20,* 11
Kampa (tremors) Su, *24,* 15
Khalli (neuralgia) Ci, *28,* 57
Khanjatva (lameness) Su, *20,* 11
Lalatabheda (frontal headache) Su, *20,* 11
Mada (intoxication) Su, *24,* 27
Moorchha (fainting) Su, *24,* 35
Mookatva (dumbness) Su, *20,* 11
Nidradhikya (hypersomnia) Su, *20,* 17
Osa (heat stroke) Su, *20,* 14
Pakshavedha (hemiplegia) Su, *20,* 11
Sankhyabheda (migraine) Su *20,* 1
Sarvangaroga (general paralysis) Ci, *28,* 29
Shirorog (diseases of the head) Su, *17,* 6
Shirastambha (cerebral thrombosis) Ci, *25,* 29
Suryavarta (recurrent neuralgic pain) Si, *9,* 79

Swarakshaya (aphonia) Su, *24*, 15
Tamasu (asthenia) Su, *20*, 11
Tamotidarsana (repeated fainting fits) Su, *24*, 15
Tandratiyoga (drowsiness) Su, *24*, 25
Timir (paralysis of vision) Su, *20*, 11
Urustambha (paralysis of thigh)
Vakbhanga (failing speech) Su, *20*, 21

Special Senses

Ear : Karnaroga (diseases of ear) Ci, *26*, 127
Karnabadhirya (deafness) Ci, *26*, 128
Karnasopha (inflammatory swelling of ear) Ci, *29*, 127
Karna Srava (pus discharge from ear) Ci, *26*, 127
Putisravana (suppuration of middle ear) Ci, *26*, 127

Eye : Aksipaka (ophthalmitis) Su, *20*, 14
Aksiroga (eye affections) Ci, *26*, 130 96 varieties mentioned
Aksibheda (squint eye) Su, *20*, 1

Nose : Nasaroga (diseases of the nose) Ci, Chapter 26
Dustapratisaya (pernicious rhinitis) Ci, *26*, 10
Ghranapaka (anosmia) Ci, *26*, 115
Nasarsas (polypus in nose) Ci, *14*, 6
Nasarbuda (tumour in nose) Ci, *26*, 116
Nasa Srava (nasal catarrh) Ci, *26*, 111
Nasasrngatka (atrophy of sense of smell) Ci, *26*, 111
Prinasa (acute rhinitis) Ci, *26*, 114
Pratinasa (obstruction to nasal passage) Ci, *26*, 112

VII Diseases of Circulatory System

Hrddrava (tachycardia) S4, *20*, 11
Hrdroga (heart disease) S4, *20*, 11
Hrumoha (heart block) S4, *20*, 11
Parsvavimarda (painful spasm in chest with dyspnoea) S4, *20*, 11
Udaravesta (cardiac pain referred to stomach) S4, *20*, 11
Dhamani pratist (dilation of arteries) S4, *20*, 177

VIII Diseases of Respiratory System

Kasa (chronic cough) Ci, *18*
Rajayakshma (pulmonary tuberculosis) Ci, *8*, 14
Svasa (asthma) Ci, *17*, 46 5 types according to symptoms

Chhinna Svasa (interrupted breathing) Ci, *17,* 54
Galagraha (acute swelling inside throat) Su, *18,* 22
Galapaka (suppuration in throat) Su, *20,* 14
Galashundaka (tonsillitis) Su, *18,* 20

IX Diseases of the Digestive System
Adhijihva (abscess under the tongue) Ci, *12,* 77
Agnimandya (dyspepsia) Su, *20,* 17
Ajatodaka (dehydration) Ci, *13,* 58
Ajeerna (indigestion) Ci, *15,* 42
Amadosha (disorder or chyme formation) Ci. *2,* 10
Amapitta (biliousness) Ci, *8,* 60
Amatisara (dysentery with mucus) Ci, *19,* 5
Amlapitta (acid-dyspepsia) Ci, *15,* 47
Anaha (acute constipation) Ci, *28,* 20
Antrapanvidah (intestinal inflammation) Su, *24,* 14
Antravridhhi (hernia) Ci, *12,* 94
Arochak (anorexia) Ci, *26,* 124
Arsa (haemorrhoids) Ci, *14,* 7
Aruchi (distaste for food) Ci, *8,* 60
Asyavipaka (stomatitis) Su, *20,* 14
Atisara (dysentery), Ci, *19,* 4
Atrupti (morbid hunger) Su, *20,* 14
Baddhagudodar (peritonitis) Ci, *13,* 39
Bhagandara (anal fistula) Ci, *12,* 96
Chhidrodar (perforation-peritonitis) Ci, *13,* 42
Grahanidosha (diarrhoea) Ci, *15,* 51
Gudabhramsa (prolapsed anus) Su, *20,* 11
Gudapaka (proctitis) Su, *20,* 14
Jalodara (ascites) Ci, *13,* 45
Jatharagnivikara (morbid appetite) Vi, *6,* 12
Kaamaala (jaundice) Ci, *16,* 34 3 types
Kumbhakaamaala (malignant jaundice) Ci, *26,* 36
Mukharoga (oral disease) Ci, *26,* 119
Raktatisara (dysentery with blood) Ci, *19,* 70
Udararoga (acute abdomen) Ci, *13,* 9
Udavarta (paralysis of intestines) Ci, *26,* 6

X Diseases of Genito-urinary System
Asmari (urinary calculus) Ci, *26,* 36 2types according to etiology
Iskshuvalikarasameha (glycosuria) Ni, *4,* 10

Medhrapaka (urethritis) Su, *20,* 14
Mutrajathara (retention of urine causing abdominal distension) Si, *9,* 30
Mutrakrcchra (dysuria) Ci, *26,* 32 8 types according to etiology
Mutraksaya (oliguria, anuria) Si, *9,* 34
Mutratita (polyuria) Si, *9,* 35
Mutrotsanga (bloody urine) Si, *9,* 34
Prameha (urinary disorders) Ni, *4,* 8 20 different varieties
Raktagranthi (tumour in bladder neck) Si, *9,* 41
Svetamutravarcastva (white urine) Su, *20,* 17
Vatasthila (hard tumour in urinary passage) Ci, *29,* 36

XI Complication of Pregnancy, Childbirth & Puerperium

Garbhiniroga (diseases of pregnancy) Sa, *8,* 26
Kshiradosa (disorders of lactation) Ci, *30,* 237
Mrtagarbha (abortion) Sa, *8,* 30
Yoniroga (diseases of the vagina) Ci, *20*

XII Diseases of Skin and Subcutaneous Tissue

Alasaka (itching red papules) Ci, *7,* 23
Charmadala (bursting eruption) Ci, *7,* 24
Charmakustha (eczema with thickened dermis) Ci, *7,* 21
Ekakustha (localized eczema) Ci, *7,* 21
Kandu (pruritus) Ci, *29,* 17
Khalitva (baldness) Su, *5,* 30
Kapala (erythema) Ci, *7,* 14
Kitima (hard, rough, discoloured dermatosis) Ci, *7,* 22
Kustha (chronic skin disease) Ci, *7*
Mandala (urticarial dermatosis) Ci, *7,* 16
Pama (mild leprosy) Ci, *7,* 25
Pundarika (ulcerated dermatosis) Ci, *7,* 18
Rsyajivhaka (suppurated dermatosis) Ci, *7,* 18
Raktapitta (purpuric eruptions) Ci, *4,* 11 7 types according to etiology
Romantika (small eruptions over entire skin) Ci, *12,* 92
Sataru (leprous sore) Ci, *7,* 26
Sidhma (psoriasis) Ci, *7,* 19
Svitra (patchy dermatosis) Ci, *7,* 173
Tvagraydarana (scaly skin) Su, *20,* 14
Udarda (urticaria) Su, *20,* 17

Viloma (alopecia) Ci, *25,* 118
Vipadika (dermatosis with fissures in extremities) Ci, *7,* 22
Visphotaka (boils) Ci, 7

XIII Diseases of the Musculoskeletal System and Connective Tissue

Asthibhanga (fracture of bone) Ci, *25,* 68
Asthikshaya (atrophy of bones) Su, *17,* 67
Chyutasandhi (dislocation of joints) Ci, *25,* 68
Gulphagraha (sprained ankle) Su, *20,* 11
Hanubheda (dislocation of jaw) Su, *20,* 11
Janubheda (bow legs) Su, *20,* 11
Januvislesa (knock knees) Su, *20,* 11
Kubjatva (hunch back) Su, *20,* 11
Kota (localised thickening of muscle) Su, *24,* 16
Mamsadaha (painful muscles) Su, *20,* 14
Mamsakleda (softening of muscle tissue) Su, *20,* 19
Padabhramsa (flat foot) Su, *20,* 11
Pangulya (deformed foot) Su, *20,* 11
Prsthagraha (stiff back) Su, *20,* 11
Urusada (artophy of thigh muscles) Su, *20,* 11
Vatabatasa (rheumatism), Ci, *29,* 11 3 types

XIV Congenital Anomalies

Ostabheda (Hare-lip) Su, *20,* 11
Vamanata (dwarfism) Su, *20,* 11

XV Certain Conditions Originating in the Perinatal Period

Nadiroga (diseases of new born babies) Sa, *8,* 45

XVI Symptoms and Signs and Ill-defined Conditions

Syndromes

Semiology or classification of diseases based on symptoms and signs was in vogue for many centuries. One of the most creative acts in Medicine has been the *detection of association of symptoms and signs* and developing them into *syndromes.* For instance Sushruta recognised the syndrome of diabetes mellitus or *"Madhumeha"* wherein he correlated the appearance of sugar in the urine (from which the disease derived its name) with the clinical symptomatology as well as causative factors:

"A person who is habituated to pampering his belly even if a previous meal has not been thoroughly digested, who is addicted to a habit of sleeping in the day or leading a sedentary life, who is averse to taking any kind of physical exercise, develops such symptoms like thirst, ravenous appetite, perspiration, fetid odours in the body, shortness of breath, dullness and heaviness in the body, inert feelings in the limbs.......he suffers from obstruction of the internal channels with deposits of fat. Hence all things or conditions which foster the growth of excessive fat should be carefully avoided." All this knowledge was based on observations, without any knowledge of underlying pathology.

Thomas Sydenham (1624 – 1699) was a great English clinician in the tradition of Charaka and Sushruta and Hippocrates. He paid great attention to the observation of signs and symptoms of disease; he studied the time-course (temporal profile) of diseases and lumped associated symptoms and signs into syndromes. He emphasised that *'natural history'* of the disease and not just isolated clinical manifestations, should be used in establishing diagnostic entities. Thus the concept of *cluster* and *temporal correlation* improved the then-existing nosology. Sydenham kept clear of theories and philosophical speculations and relied mainly on observations, including response to specific therapy, such as response to cinchona bark in identification of malaria, response to colchicine in identification of gout, and response to mercury in the identification of a syphilitic lesion. By considering the temporal profile and natural history, Sydenham descriptively separated gout from rheumatism, and the cluster of measles and scarletina from other exanthemata. He identified several other clusters like "Syndenham's-chorea"' or Saint Vitus' dance, and quartan malaria.

Relying on clinical manifestations alone, Sydenham's successors in the 18th Century developed elaborate nosologies to classify "disease" according to arbitrary clusters of symptoms and signs.

Carl Linnaeus (1707 – 1788) was a Swedish doctor and professor of medicine, but his versatility extended to many other branches of natural science such as botany, zoology, geology and minerology. His publication *"Systema Naturae"* in 1735 created a new era in the history of natural sciences. Linnaeus was a great classifier. In both his famous works, *Systema Natura* and *Species Plantarum,* he introduced the binary system of nomenclature for plants and animals. He gave each species a name consisting of two words, a generic name and a specific name, which represented a major simplification and precision in terminology. After creating an effective observational taxonomy for botany and zoology, Linnaeus produced a medical classification system that had 11 major categories and 325 subdivisions of clinical "diseases". One of his treatises was entitled *General Morborum.*

Francis Bossier de Lacroix (1706 – 1777), better known as Sauvages, used similar approach to attempt a classification of diseases systematically. His comprehensive treatise was published under the title *Nosologia Methodica.* It contained 10 major classes, subdivided into 44 orders, 315 genera and 2400 species, all based on signs and symptoms.

William Cullen (1710 – 1790) of Edinburgh, published a classification of diseases in 1785 under the title *Synopsis Nosologiae Methodicae.* Cullen tried to simplify clinical nosologies by giving greater attention to internal logic in selecting categories and by making a Sydenham-like attempt to distinguish individual symptoms and signs from "diseases".

The main defect of the 18th century nosology was that it was an intellectual construction that depended on clusters but not on correlations, either in time-course or underlying morbid anatomy and pathology.

The Impact of Anatomy on Classification

The Renaissance Period in Europe (1500 – 1700) witnessed an extraordinary flowering of intellectual activity. The period was characterised by the liberation of the intellect from the shackles of traditional dogma and established authority. The past was no longer supreme and truth was not necessarily all that was given in the ancient books, but something which should be ascertained by direct observation and experiment. Unquestioning acceptance of authority gave way to criticism and experimental enquiry.

In the same year (1543) that Copernicus made his revolutionary observations in astronomy, Andreas Vesalius (1514 – 1564) published

"Fabrica Humani Corporis" or Structure of the Human Body. Sir William Osler in this Century described it as the greatest book ever printed from which modern medicine dates. Vesalius was interested in anatomy, and while still young dissected animals like mice, rats, cats and dogs. He wrote: "My study of anatomy would never have succeeded had I, when working at medicine at Paris, been willing that the human viscera should be merely shown to me and to my fellow students at one or another public dissection by wholly unskilled barbers, and that too in the most superficial way. I had to put my hands to the business".

In 1537 Vesalius was appointed Professor of Anatomy and Surgery at the University of Padua. He did dissections with his own hands and taught only what he could observe himself in the structures of the human body, and not what Galen had written in the first century A.D. Thus Vesalius ushered the era of medical science based on observation of facts rather than traditional descriptions, based on speculations.

Concept of Morbid Anatomy

Leonardo da Vinci (1452 – 1519) was a multifaceted genius, an artist, sculptor, scientist, architect, geologist, physicist, mechanical engineer and a biologist, all in one. Leonardo performed many dissections on the human body with a marvellous anatomic technique. He used injections into veins, liquid wax in arteries, and made gross serial sections to study structures of the body and drew beautiful diagrams of the appearances he observed. He studied muscles and bones, made sections of the brain, traced the cerebral veins and studied many other aspects of anatomy. Although his work did not attract much attention at the time, the following passage shows his seminal contribution in extending medical thought. He wrote:

"And this old man, a few hours before his death, told me that he had lived a hundred years and that he did not feel any bodily ailment other than weakness. And thus while sitting upon a bed, without any movement or sign of anything amiss he passed away from this life. I made an autopsy in order to ascertain the cause of so peaceful a death, and found it proceeded from weakness through failure of blood and of the artery that feeds the heart".

The correlation of morbid anatomy with the understanding of disease was a major step in the history of medicine. Because of the lack of appreciation of the relation of anatomy to pathology the ancient

Greek physician Philinus of Cos, a pupil of Herophilus, a follower of the Hippocratic school lamented: "All the anatomical knowledge I have derived from Herophilus has been useless to me in treating the sick".

Clinico-pathological Correlation

Giovanni Battista Morgagni's (1682 – 1771) magnum opus, "On the sites and Origins of Disease", published in 1761, was a landmark in the history of medicine and an important step ahead in the classification of diseases. Morgagni was by no means the first to make morbid anatomical observations, but he was the first to make systematic and meticulous *correlations of symptoms and clinical findings* in 640 case records, *with the morbid anatomic findings at autopsy.* From now on, clinical records took new meaning by being linked with the knowledge (and therefore prediction from symptoms during life) of abnormal appearances in the viscera. Moreover, since Morgagni wrote as a clinician, and headed each of his letters by symptoms rather than morbid anatomy, his work was easily appreciated by the clinicians.

In a letter, "which treats of epilepsy", he describes a fellow citizen, a grave and worthy priest in his 68th year, "who was seized with an epilepsy which left behind it the greatest slowness of the pulse". Morgagni had the intellectual honesty and courage to confess that he could find no satisfactory morbid anatomical cause for the sỳmptoms. In the latter part of the 20th century, the patient would be recognized as suffering from "sick sinus syndrome", with extreme bradycardia and cerebral ischaemia causing the convulsions, and would be put on a permanent pace-maker.

From Morgagni's days onwards, the word diagnosis took on a new meaning; the location of the site of origin of the patient's symptoms became an essential part of the diagnostic concept. Thus the site and size of the thoracic and abdominal viscera, both in health and in illness, became of prime importance to the clinician. No longer could the clinician claim that anatomical knowledge was useless in the management of the sick people. Furthermore, the search for clinical methods of examining the body which might give information about the state of the thoracic viscera was begun by Leopold Auenbrugger in 1761, the same year as Morgagni's publication. Auenbrugger wrote: "I here present the reader with a new sign which I have discovered for detecting diseases of the chest. This consists in percussion of the human thorax, whereby according to the character of the particular sounds thence

elicited, an opinion is formed of the internal state of that cavity''. Sound, he revealed, could bring information of parts which could not be reached by sight of the eye, for example the thoracic cavity.

Auenbrugger's work was neglected during his time but revived in 1808 by Corvisart, Napoleon's physician. Corvisart, founder of the Parisian School of Morbid Anatomical Medicine, applied Morgagni's method to diseases of the heart. He differentiated various valvular lesions, made a distinction between hypertrophy and dilatation, and distinguished hydrothorax consequent on heart failure from primary pleural effusion. He wrote: "It is clear that the majority of the individuals reputed to have died of anasarca and particularly of hydrothorax, and of various species of asthmas and singular dyspnoeas, may have perished from diseases of the heart."

Laennec in 1819 introduced the method of mediate auscultation. It was purely a chance discovery, in no way an outcome of the knowledge of the physical laws of sound, nor for many years were the findings of auscultation satisfactorily explained in terms of physics. But Laennec made anatomic sense of sounds, correlating the auscultatory findings in the chest with disease of the underlying lung. He recognised tuberculosis as a single disease, and identified the abnormal liver anatomy of cirrhosis.

Adams, Cheyne, Corrigan, Graves, Parkinson, Stokes were the other great Irish and British patho-clinicians who joined the French, German, Viennese and other European patho-clinicians who provided clinico-pathological correlations for nosology.

Bichat (1771 – 1802) extended the organ concept of disease to the tissue level. Pinnel and Bichat, the two Frenchmen began a consistent system of anatomic correlation for "disease". A diagnostic nomenclature based on correlation with pathologic anatomy immediately removed two of the many obvious scientific disadvantages of the preceding clinical and etiologic classifications. The "etiologic" concepts of classification were speculative (for instance "excess" of Vata, or "decrease" of Kapha), unaccompanied by verifiable, observable evidence. The "clinical" concepts were based on observation, and often consisted of only a patient's subjective feelings. Anatomic pathology provided correlation with what was observed clinically. The very word "dis-ease" which had originated as an expression of the patient's abnormal sensations, now often was used to designate an abnormality of gross or microscopic structure. Until that moment in the history of science, astronomers were the only few scientists who could

confirm their experimental reasoning merely by observing nature. Now, after observing the symptoms and signs at the bedside the clinician too could make a scientific prediction (diagnosis) during life, of what the pathologist would find post mortem in the organs, tissues or cells.

Concept of Patho-physiology

During the time of Vesalius, Padua was an enlightened seat of learning and it was here that Galileo Galilei (1564-1642) designed and worked with his telescope and laid the foundation of a new era of experimental scientific studies. Although he studied medicine for some time at Pisa, Galileo was essentially a mathematician and laid great stress on exact measurement. The experimental spirit of Galileo greatly impressed the Englishman William Harvey (1578-1657) who studied medicine in Padua in 1602. Harvey demonstrated that blood circulates in the body, thereby ushering the era of experimental method in medicine. In his famous book "Exercitatio Anatomic de Motu Cordis et Sanguinis in Animalis", he wrote: "I frequently and seriously thought, what might be the quantity of blood which was transmitted, in how short a time its passage might be effected, and the like; and not finding it possible that this could be supplied by the juices of the ingested aliment without the veins on the one hand becoming drained, and the arteries on the other hand becoming ruptured through the excessive charges of blood, unless the blood should somehow find its way from the arteries into the veins and so return to the right side of the heart; I began to think whether there might not be a motion, as it were, in a circle. Now this I afterwards found to be true and I finally saw, that the blood forced by the action of the left ventricle into the arteries was distributed to the body at large and its several parts, in the same manner as it is sent through the veins and along the vena cava, and so round to the left ventricle in the manner already indicated, which motion we may be allowed to call circular".

"Since all things, both arguments and ocular demonstration, show that the blood passes throughout the lungs and heart by the action of the ventricles, and is sent for distribution to all parts of the body it is absolutely necessary to conclude that the blood of the animals is impelled in a circle and is in a state of ceaseless motion, that this is the act or function which the heart performs by means of its pulse; and that it is the sole and only end of the motion and contraction of the heart".

To us it is perhaps surprising that Harvey did not attempt to define

the clinical effects of the heart's failure as a pump, but he justified his reluctance to enlarge on all such matters, even the function of circulation, by the remark: "Our first duty is to inquire whether the thing be or not, before asking wherefore it is". Harvey did, however, in fact give a good account of left and right ventricular failure in his friend Sir Robert Darcy, who, "when he had reached the middle period of life made frequent complaint of a certain distressing pain in the chest so that dreading at one time syncope, at another time suffocation in his attacks, he led an unquiet and anxious life. The disease, going on from bad to worse, he by and by became cachectic and dropsical and died in one of his paroxysms. In the body of this gentleman we found the wall of the left ventricle of the heart ruptured".

Wunderlich and other Germans urged that *pathological physiology* be the true basis of medical science. One group of pathologic physiologists, led by Rudolph Virchow, concentrated on delineating causes and mechanisms of disease at the *cellular level*—cellular pathology.

Another group of pathologic physiologists, led by Claude Bernard concentrated on function. Before the end of the 19th Century Bernard and many others had begun to reject the nosology of morbid anatomy for its failure to identify abnormal function. With the advances in biochemistry it became evident that biochemical lesions preceded structural changes and hence may not be detected by morbid anatomy alone (See chapter on "Nutrition"). The increasing array of modern laboratory tests have identified physiologic and biochemical disorders, etiologic agents and many other aspects of disease that cannot be detected from observations of morbid anatomy. Clinical chemistry is a new medical specialty for dealing with many of these tests.

In a pioneering effort to improve clinical diagnostic nomenclature the New York Heart Association in 1965 established a system for classifying etiology, anatomy, physiologic function, and clinical consequences, in the diagnosis of heart disease. As an illustration, let us follow the intellectual process of a Cardiologist when he examines a patient with the symptoms of shortness of breath or angina pectoris. The *sensation* described by the patient is the actual phenomenon perceived by the patient himself, such as discomfort in the chest. By clinical interrogation the cardiologist provides *specification,* that is, adds further characteristics such as substernal location, aggravated by exertion, relieved by rest. The next intellectual step is *designation*—the cardiologist gives a name to the specified sensation—angina pectoris. The

next intellectual step is to make an *inference* about the underlying structural abnormality—Coronary artery atheroscelerosis.

Similarly the *first order* classification of the *symptom* such as dyspnoea on exertion, is developed into a *second order* of classification, a *syndrome* of congestive failure by clustering all symptoms and signs such as pulmonary basal crepitations and swelling of the feet; and then into a *third order* of classification—*inference* about the *underlying structural abnormality* responsible for the congestive heart failure, such as mitral stenosis, or congenital heart disease; the *fourth order* of classification is an *inference* about the *etiology:* rheumatic valvular disease or maternal rubella infection. The *fifth order* of classification is the *functional status* of the patient—based on observed effort tolerance.

It is worth noting that all the *inferences* are based on verifiable evidence and not on philosophic speculations.

The clinician of today is fortunate in having detailed information about altered anatomy, physiology and biochemistry in the patient through clinical chemistry, endoscopy, radiology, electrophysiology (ECG, EEG, EMG), ultrasonography, gamma scintigraphy, computerised X-ray tomography and NMR imaging. He can thus correlate and integrate the signs and symptoms with altered anatomy, physiology and biochemistry and pathology. In the absence of such an integration, the present day practitioners of Ayurveda or Homoeopathy must find themselves in the same predicament that Philinus of Cos was in, two thousand years ago.

Problems in Disease Classification

The American College of Pathologists has presented a nomenclature and classification of diseases on the basis of four modalities; topology, morphology, etiology and function. The main defects of the pathologists' taxonomy are its omissions, not its contents. For example, gout, syphilis, haemophilia, diabetes mellitus, systemic lupus erythematosus are examples of *non-topographic, non-morphologic* diagnosis involving *multiple organs or systems,* with multiple clinical syndromes, and the diagnosis is based on laboratory support. Myasthenia gravis is the name of a symptom; erythema nodosum and hypertension are names of physical findings; some of the non-morphologic diagnoses represent a straight-forward classification of observed para-clinical evidence, for example porphyria, hyperglycaemia, hypertriglyceridemia, or proteinuria; or the physiological diagnosis of paroxysmal atrial tachycardia with 3:1 block, or "sick sinus

syndrome''. Chronic alcoholism and drug addictions are names of habits; renal failure, hepatic failure, "irritable bowel", imply physiologic dysfunction resulting from diverse etiological factors.

Disorders of the Cell

Since the cell is the functioning unit of life, all disease is the result of damage, disablement and malfunction of the cells and tissues of the body. According to our current understanding, disorders of the cell can arise from genetically determined defects, lack of essential nutrients, adverse physical environment, harmful substances or living agents causing injury. The various mechanisms whereby injury could be caused are listed in Table II.

TABLE II

Disorders of the Cell

I. *Genetically determined defects*
   Point mutations – defects in proteins & enzymes
   Visible changes in Karyotype

II. *Lack of essential nutrients*
   Poverty of diet
   Defective absorption of nutrients
   Deficiency of internal secretions
   Interruption or retarded supply of blood – ischaemia, infarction
   Defective penetration of nutrients into cells

III. *Adverse Physical Environment*
   Trauma
   Heat
   Cold
   Ionizing radiation
   Electrical shock

IV. *Harmful Substances*
   Direct action on cell architecture
   Interference with enzyme action
   Lethal synthesis
   Carcinogenesis
   Antigenic action

V. *Living Agents*

A. Injury by cells of the body itself
   Depriving other cells of essential nutrients
   Liberating or forming harmful substances
   Forming antibodies or sensitizing cells that subsequently cause damage by reacting with antigen

B. Injury by parasitic cells
   Depriving other cells of nutrients
   Liberating harmful substances, exotoxins, endotoxins
   Harmful antigenic actions – lymphokines
   Intracellular growth.

Molecular Disease

The conceptual union of genetics and metabolism is perhaps the most fruitful development in biologic science of the past decades. Sir Archibald Garrod's monograph "Inborn Errors of Metabolism" published in 1909 marked the beginning of the era of biochemical genetics, and the concept of biochemical lesions. Direct evidence that human mutations actually produce an alteration in the primary structure of proteins was first obtained in 1949 by Linus Pauling and his associates, by their studies on sickle cell haemoglobin. The subsequent study of Ingram established that the electrophoretic abnormality arose beccause HbS had a valine substitute for glutamic acid residue at number 6 position in the amino-acid sequence. Thus the fact was established that inborn errors of metabolism were caused by mutant genes that produced abnormal proteins whose functional activities were altered.

Biochemical Lesions

All injuries, whether mild or lethal, ultimately occur at a biochemical level beyond our present range of detection. Four intracellular systems are thought to be particularly vulnerable: (1) aerobic respiration involving oxidative phosphorylation and production ATP, (2) Synthesis of enzymic and structural proteins, (3) maintenance of the integrity of cellular membranes on which the ionic and osmotic homeostasis of the cell and its organelles are dependent, and (4) preservation of the integrity of the cells' genetic apparatus.

Whatever the precise point of attack, injury at one locus leads to wide-ranging secondary effects. Because maintenance of the ionic and fluid balance of the cell is energy-dependent, impairment of aerobic

respiration and the synthesis of ATP soon lead to profound alterations in the intracellular content of ions and water. Loss of aerobic respiration is usually followed by reversion to anaerobic glycolysis with the production of excessive amount of lactic acid. The falling pH has secondary effects on enzyme systems and biochemical reactions. Protein synthesis is impaired, preservation of membrane integrity hampered, and progressive cellular dysfunction ensues. Such a sequence of biochemical events does not occur instantaneously. It is a dynamic process which evolves over a period of time from minutes to hours. The precise time span involved depends on the particular characteristic of the injured cell, such as its metabolic activity and vulnerability to a specific lesion as well as the defensive mechanisms of the organism as a whole. Morphologic changes become apparent only after some critical biochemical system within the cell has been deranged for some time.

The Full Circle

The searching human mind has always tried to delve deeply into the "whys" and "wherefores" of disease. The search for causes and mechanisms is continuous, for therein lie the origins of the pathophysiology of disease and the implications to the patient and the physician. In the 20th century the focus is on biomolecular and ultrastructural origins of disease and the evolution of the cellular and tissue alterations from their incipiency to their full-blown stages of development. In this way diseases are presented as dynamic processes changing with time, modified by therapy and by host and invader adaptive responses all having effect on the ultimate clinical manifestations.

It must be accepted with humility that there are gaps in our knowledge and much is still unknown, hence the search for greater understanding is unending.

It is interesting to see the full circle that medical science has taken in 2000 years. Conceptually, Charaka and Sushruta thought of disease as disequilibrium of normal body constituents (of the three *doshas*) and restoration of that equilibrium as the objective of medicine. Although their thinking was purely intuitive and speculative, they dealt with health and disease at a molecular level. In the reductionist approach of experimental medicine, we went from the whole person to the level of individual organs and tissues and looked for specific causes. When we reached the level of the cell and subcellular organelles the doctrine of specific causes becomes blurred, because various types of insults may produce the same result in terms of biochemical lesions. In future

classification of disease we might emphasize what underlying disturbance of control mechanism we are treating rather than treating a given disease.

Holistic Approach and Disease Classification

Another criticism of the reductionist biological approach to disease classification is becoming more and more vociferous in the rising tide of "holistic medicine". Doctors primarily deal with patients as *persons* while the medical taxonomy classifies them into *diseases.* It has been well said, "there are no diseases, there are only sick persons". Feinstein has in recent years written extensively to advocate the need for a *clinical taxonomy* as distinct from the taxonomy of morbid anatomy, that was initiated 200 years ago. He says, "In preserving the diagnostic nomenclature of pathological anatomy as the main contemporary system of identifying human ailments, clinicians perpetuate a mode of thinking that classifies disease but not people or illness; and that classifies clinical inferences, but not clinical observations". A clinician's nomenclature must classify a *host,* and an *illness* and a *disease.* A clinician must have a language that will categorize the variations in human clinical behaviour, and the nuances of human response to sickness and to therapy.

The WHO Reason-for-Encounter Classification

Most classifications are designed to classify the interpretation, by the healthcare provider, of a patient's illness, disease or injury. In 1978 a working party of experts, both in primary healthcare and in classification systems met in Geneva. After several years' work they produced a Reason-For-Encounter Classification (RFE-C), which classifies the reasons for seeking healthcare from the perspective of the patient. The reasons for the encounter are those given by the patient before the physician or other health worker makes any judgment as to their validity or accuracy. It is thus patient-oriented rather than disease or provider oriented.

The classification is designed along two axes:

Chapters and components: Most chapters cover the body systems; others are non-anatomical and are entitled "general", "psychological" and "social". Infectious diseases, neoplasms, injuries and congenital anomalies do not form separate chapters as they do in the International Classification of Diseases, 9th revision (ICD-9), but rather are represented in the diagnosis/disease component of each

chapter. Each chapter is subdivided into the same seven components:

1. Symptoms and complaints.
2. Diagnosis, screening and preventive procedures.
3. Treatment procedures and medications.
4. Test results.
5. Administrative.
6. Others.
7. Diagnoses and diseases.

The use of one and the same classification first to identify patient demand and then to classify the result of the health care providers' interpretation and intervention could significantly improve the quality of information available concerning the use and appropriateness of health care services at the primary level.

In India there are 200,000 practitioners of modern medicine and more than 500,000 practitioners of Ayurveda and Homoeopathy. All of them can use the "reason for encounter" classification, which will give health planners in India a useful data base essential to the planning, implementation and evaluation of services for the prevention and treatment of disease and to the setting up of priorities among these services. It may result in a more intelligent structuring of the primary health care.

Classification of Human Types

Attempts to classify people according to their physical and mental attributes are quite ancient. Ayurveda classifies human constitution into three types, namely the *Vata Prakriti,* the *Pitta Prakriti* and the *Kapha Prakriti.* No true *mono-doshic* individual exists. Therefore it is the general predominance of the activity of a particular *dosha* in an individual that decides his type and not the absence of the other *doshas.* The *doshic* manifestations themselves are twofold, healthy and unhealthy. Enthusiasm and fear, courage and anger, cheerfulness and dullness exemplify the respective healthy and unhealthy manifestations of the three *doshas, Vata, Pitta and Kapha,* on the psychic plane. Similarly physical agility respectively and lightness of the limbs on the one hand, and pains and aches in the body on the other, are both *Vata* characteristics.

Hippocrates described the habitus phthicus and habitus appoplecticus. Kretchmer described the pyknic or athletic and asthenic types. In the 19th Century "Vagotonic" and "Sympathotonic" types of personalities were described and in the 20th Century we talk of "Type

A" and "Type B" personalities. In the 20th Century systematic, objective and reproducible measurements of the human physique have been made by Sheldon, Draper, Tanner and Dupertuis; somatotyping as the science is called, has demonstrated interesting relationships between somatotype and disease, both physical and mental. Tuberculosis is more common in "ectomorphs" while cancer seems to spare high ectomorphs.

Somatotyping:

Somatotyping is an estimate of body build or physique. The physique is measured in terms of its shape and the relative preponderance of structures developed from the three layers of the germinal plate—the endoderm, the mesoderm and the ectoderm which form its three basic components. The guts and the viscera are developed from the endoderm and predominate in those with dominant endomorphy, the muscles and bones are developed from the mesoderm and predominate in mesomorphy, the skin and nervous system are ectodermal structures and are well developed in the predominant ectomorph.

Somatotyping recognises the continuous variation in the degree of development of these three components in different persons, and in different regions of the same body. Each component, endomorphy, mesomorphy and ectomorphy is graded from 1 to 7 in a seven-point scale. Each physique consists of some degree of each component and 1 represents the minimum development, 7 the maximum and 4 the mid-position of each component. Sheldon has found that in the natural distribution of human physique the sum of the three component numerals varies from 9 to 12, and there are more 10's and 11's than 12's and 9's. If a physique has 7 in one component, it cannot have more than 4 in any other; if one has 6 in one, not more than 5 in another and even rating of 5 in two of the components is very rare in natural distribution of men. In terms of one rating as a unit there are 88 known somatotypes. If ½ rating is used as a unit in a scale of 1 to 13, then there are more than 400 somatotypes *(Fig. 4.1)*.

Somatotyping of 5 regions head and neck, thorax, upper limbs, abdomen, lower limbs may show varying degrees of dysplasia or disproportionate development.

In terms of maleness or femaleness, a rating of 1 to 7 can be given with android and gynoid types at extreme ends *(Fig. 4.2)*.

Somatotype is estimated from carefully posed, full-length photographs in 3 views—anterior, posterior and left lateral, taken in

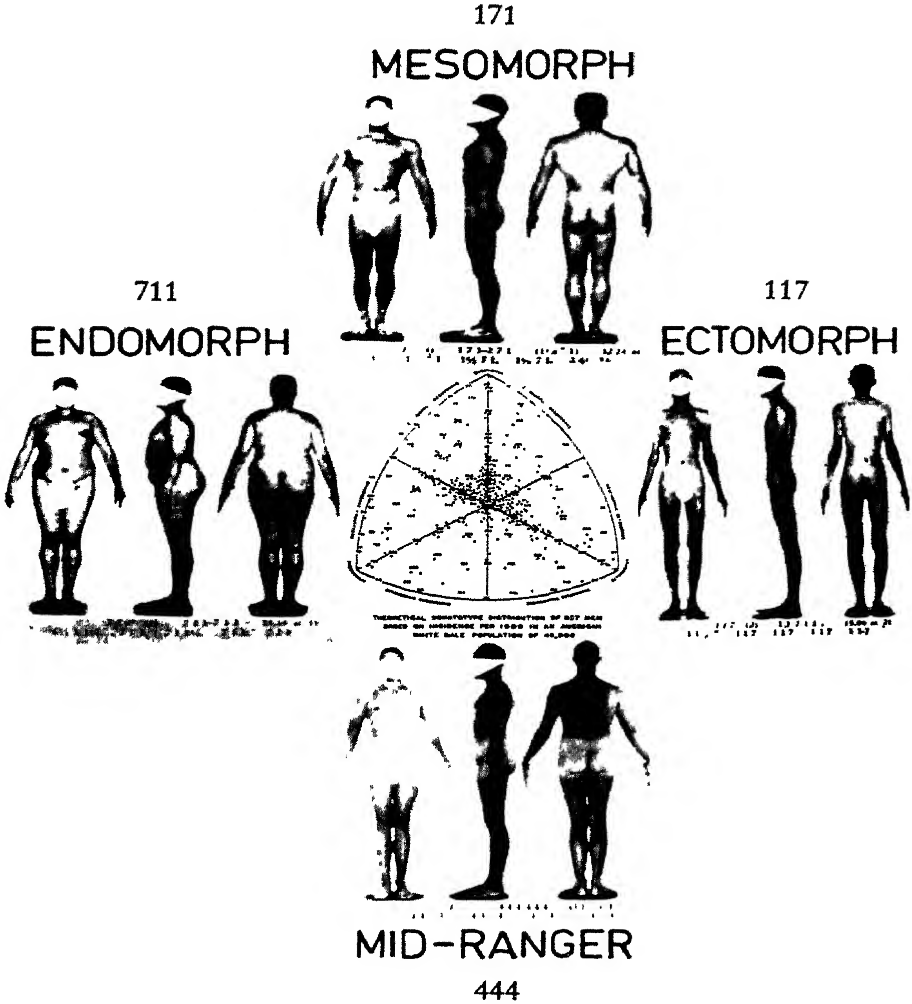


Fig. 4.1 Examples of extreme ECTOMORPH (117), MESOMORPH (171) and ENDOMORPH (711). Most physiques fall in MID-RANGER (444) as shown in the Scatter diagram.

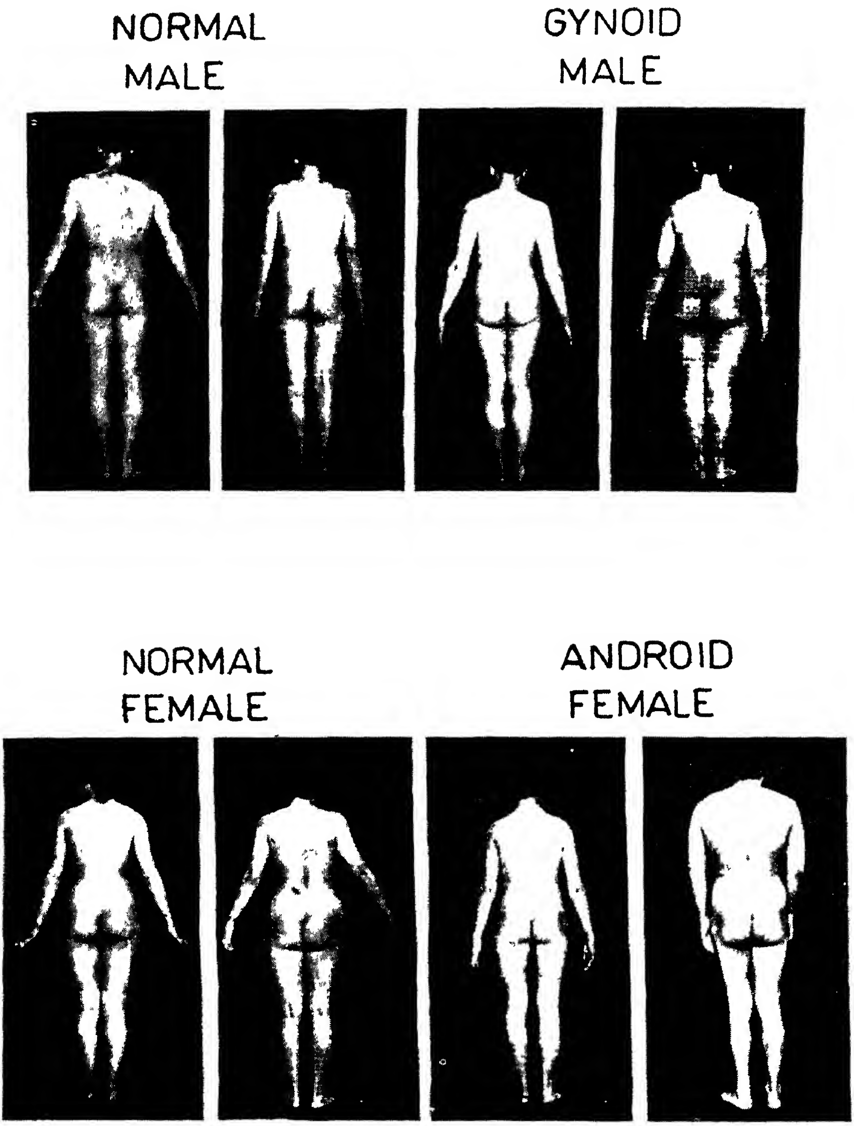
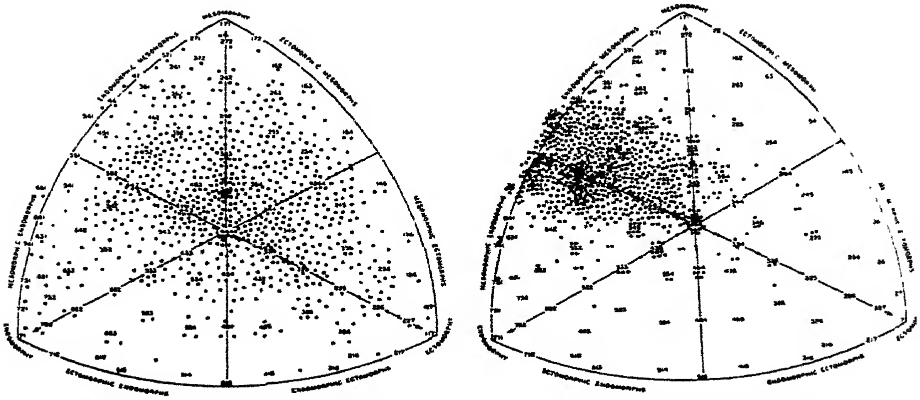


Fig. 4.2 Showing examples of NORMAL MALES and GYNOID MALES (upper row), and NORMAL FEMALES and ANDROID FEMALES (lower row).

the nude or near nude and from estimating the ponderal index from the height/Cuberoot of weight. Tanner has shown that with some training, observer error between two observers and in the same observer at different times, is not more than half a rating in 90% of the cases.

In a recent study of 800 patients at the Cleveland Clinic in USA, who had recovered from "heart attack" (myocardial infarction), Dr. Wesley Dupurtuys noted a striking predominance in endomorphic mesomorphs—as shown in Fig. 4.3. Some examples of physiques more prone to "heart attacks" are given in Fig. 4.4.



THEORETICAL SOMATOTYPE DISTRIBUTION OF 837 MEN BASED ON INCIDENCE PER 1000 IN AN AMERICAN WHITE MALE POPULATION OF 46,000

SOMATOTYPE DISTRIBUTION OF 837 MALE WHITES WITH ASHD

Fig. 4.3 Comparison of NORMAL POPULATION (left) with patients of MYOCARDIAL INFARCTION (right) showing predominance of endomorphic mesomorphism.

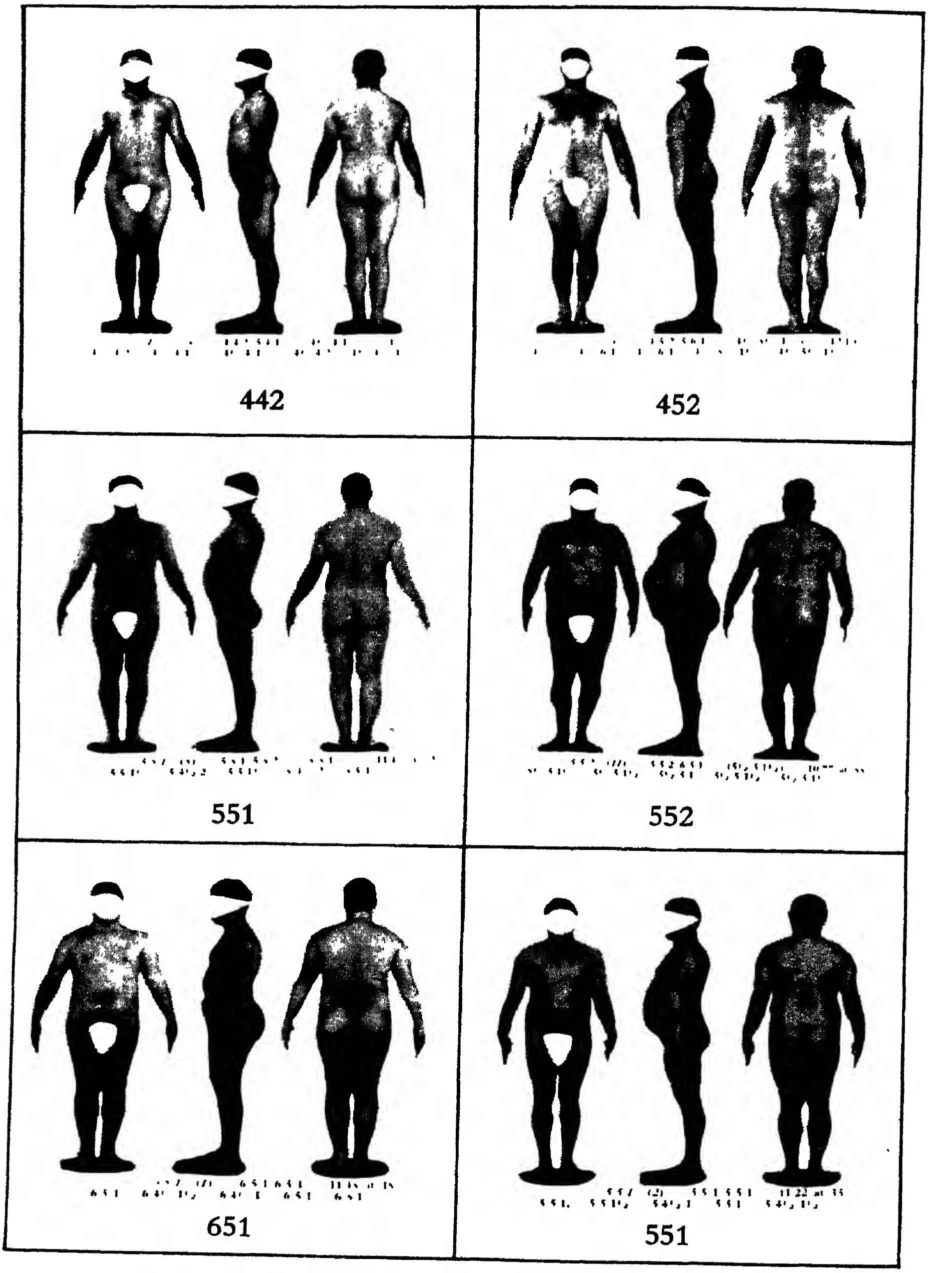


Fig. 4.4 Showing some examples of physiques prone to "HEART ATTACKS".

The extreme endomorph 711 is rounded and shows the maximum mass for minimum surface area. His head and trunk are rounded, the trunk, abdomen and pelvis have the maximum mass, the limbs are heavy proximally and taper peripherally into small hands and feet. Bones and muscles are poorly developed and all contours are mounded by abundant fat. The skin is soft and delicate. The viscera are large and weigh more than in the other types.

The extreme mesomorph 171 shows the greatest development in muscles and bones. The head is square shaped and massive, the neck is thick, the chest broad and square shaped, the abdomen and pelvis comparatively small, the limbs are heavy and large throughout and end in massive hands and feet. Muscular contours stand out throughout, the skin is thick and firm.

The extreme ectomorph 117 is thin and fragile and has maximum surface area for minimum mass. The body is linear, the limbs long and thin, right upto the hands and feet, the chest and abdomen are thin and flat, the shoulders are rounded, the scapular stand out of the neck just forward to support the head, the face is triangular.

The somatotype is genetically determined, though its full manifestation occurs only after puberty which is the proper time to assess the type. Different races show predominance of one or the other component. On the whole, in cold climates there is higher mesomorphy though some of the polynesians show high mesomorphy. Exercise cannot increase the mesomorphy though the estimate may be improved by half a rating and wasting due to malnutrition cannot convert an endomorph or a mesomorph into an ectomorph as it is still possible to detect the basic physique. Women are on the whole more endomorphic and will rarely show extremes of mesomorphy or ectomorphy met with in men.

There is little information on the biochemical counterparts and determinants of the somatotypes. For every degree of rise in endomorphy, there is an average increase in serum cholesterol by 11mg%. Persons with effort syndrome show blood lactate levels higher than normal males. Women have higher blood lactate levels after exercise than males, significantly effort syndrome is common in gynandromorphic males.

Sheldon and his colleagues have observed a close relationship between phýsique and temperament. The *viscerotonic* temperament loves comfort and relaxation, eating and sleeping, is tolerant and complacent,

craves for affection and approval and needs people when troubled. This is seen in dominant endomorphy.

The *somatotonic* temperament is assertive, energetic, forthright and unrestrained.

The *Cerebrotonic* temperament is restrained, sociophobic, loves privacy, sensitive of feeling, needs solitude when troubled; this is seen predominantly in ectomorphs.

Paranoid schizophrenia tends to occur in mesomorphs and hebephrenic schizophrenia in high ectomorphs. Dysplasia and gynandromorphy are high in schizophrenics.

It is perfectly feasible to judge by inspection (somatoscopy) the predominant primary component and the secondary component. In clinical examination ten types can be commonly used to describe patients: (1) *ectomorph,* (2) *mesomorph* and (3) *endomorph* can be used to describe those in whom the other two components do not each exceed an estimated rating of 2, (4) *endomorphic mesomorph,* (5) *ectomorphic mesomorph* (6) *ectomorphic endomorph,* (7) *mesomorphic endomorph,* (8) *mesomorphic ectomorph,* (9) *endomorphic ectomorph*—in these the main component has a rating of 5 or 6 and the secondary component 3 or 4 and (10) *Midranger* in whom all the three components lie between 3 and 4. Along with height and weight it will give the requisite information about physique. This should replace the current height, weight and "ideal weight" tables.

Recent Advances in Taxonomy

Charaka states: "A classifier may classify a subject admitting of classification in one particular way. Reclassifying his subject over and over again with reference to other differentiating factors, he is able to achieve a fresh classification each time. A subsequent classification does not repudiate the validity of the previous one".

In the above statement of Charaka, we find a profound basic truth about classification theory, the distinction between *monothetic* and *polythetic* classification, clearly enunciated in modern times by Beckner. Monothetic classifications are those in which the classes established differ by at least one invariant property which is uniform among the members of each class. Such classifications are especially useful in setting up taxonomic keys and certain types of reference and filing systems. Polythetic classifications are those in which the taxa are groups of individuals or objects that share a large proportion of their

properties but do not necessarily agree in any one property. No single uniform property is required for the definition of a given group nor will any combination of characteristics necessarily define it. This somewhat disturbing concept is readily apparent when almost any class of objects is examined, including human beings.

A corollary of polythetic classification is the requirement that many properties (characters or indicants) be used to classify objects. This is true of almost any type of objects being classified. Once a classification has been established, few characters are generally necessary to allocate objects to the proper taxa, or identification. Initial classifications based on few characters usually have to be modified once information on additional characteristics was acquired. Diseases not differentiated in earlier times now represent separate clinical entities with the accumulation of new knowledge.

A convenient way of developing classifications is to compute functions that yield similarities or dissimilarities (distances) between all objects taken two at a time. A symmetric matrix of such similarity or dissimilarity coefficient is then analysed to represent their relationships as *clusters.* Much recent progress in classification has consisted of devising methods of clustering. Properties of clusters include their location in an "n" dimensional space (some measure of central tendency), their dispersion, their shapes, their connectivity and the magnitude of gap between clusters. Clustering algorithms can be agglomerative or *divisive. In most clustering techniques especially in polythetic* methods, the agglomerative approach is preferred for practical reason in devising a workable computer algorithm.

The whole idea of hierarchic, non-overlapping (mutually exclusive) classification which has been so attractive to the human mind is currently undergoing re-examination. The acceptance of polythetic taxa is a major conceptual advance. Computer techniques of cluster analysis and ordination have been successfully applied to a broad range of disciplines, and it is very desirable that it should be extensively applied in Medicine.

Chapter 5

MATHEMATICS IN MEDICINE

Introduction

Medical knowledge consists largely of an impressive collection of empirical data, much of which has resulted from careful observation and investigation of patients. Medicine still does not have the coherent structure of a fully developed science. In the physical sciences, mathematics has been the foundation upon which a scientific structure has been built. Unfortunately biologists in general and medical men in particular have been hesitant to fully utilize mathematics in the solution of their problems. The impact of the computer revolution in the last two decades has changed all this. The development of decision theory and computers has now made it possible to consider the development of a logic or calculus of medicine using mathematical methods, mathematics being defined as the manipulation of words & symbols in accordance with precise rules.

In its broadest sense, mathematical symbolism is a method of describing relationship of things that people think about. Each symbol represents a thing or a property called *variable* and the arrangement of symbols shows how these variables are related to one another. In biology and medicine, mathematics provides different types of organizational arrangements for different variables, examples of which will be discussed later.

Professor Wilfrid Card of Glasgow along with Jack Good, an outstanding mathematician, wrote in 1973 about the mathematical structure of Clinical Medicine. Later, they wrote on "Logical Analysis of Medicine" based on mathematical thinking. I have quoted extensively from their published work in view of the importance of their ideas.

Mathematical Ordering of Data

A doctor measures the height, weight, pulse rate, respiration rate, temperature, blood pressure, chest girth and abdominal girth etc. of

the patient. These are *dimensional measurements* or *mensurations* of continuous variables. Ordering of two comparable dimensions is done very simply, and its equations are depicted by the familiar symbols: ($>$) greater than, ($<$) less than, and ($=$) equal to.

To depict the dependency of two or more continuous variables, mathematical procedures provide the equations of straight lines or curves that represent the dependent relationship between one continuous variable and another (e.g. effect of age on blood pressure). The variables are continuous because they can extend through an indefinite range of numerical values; the relationship is dependent because each value of one variable corresponds to at least one value of the other as changes occur. The equations for such relationships can be simple or complicated, and are provided by the binomial and polynomial structures of algebra, analytic geometry and the calculus. The analog computer measures dimensions and its circuits use the differential and integral equations of continuous variables.

In medicine, many variables are *non-dimensional* and *discrete,* such as sex, race, colour of eyes, and clinical data like symptoms and signs, which are verbally described. The new mathematics of *set theory* and *Boolean algebra* is used to measure such discrete, multiple, independent variables. The circuits of modern digital computer use the Boolean logic (yes or no, one or zero, true or false). The individual attributes of the patients which are described verbally, can now be expressed in numerical form as the sums of counted patients or of counted attributes, that cannot be dimensionally measured.

An important mathematical application in medicine relies largely on *statistics* and *probability theory,* two fields which have been developed to study non-deterministic processes, i.e. processes in which an exact cause and effect relationship does not exist. In most biomedical investigations, multiple factors influence the particular parameters of interest. For example, although it is impossible to predict the course of illness of a specific patient, generalizations can be made to describe a large population of such patients.

Vital statistics and health statistics reflect the health of the community in much the same way as records of temperature, pulse and respiration reflect the health of the individual. From the population census, and records of births, marriages and deaths, calculations are made of live birth rates, infant mortality rates, maternal mortality rates, crude death rates, life tables giving expectation of life and probability of dying before the next birthday etc. Thus has developed the

science of *demography,* the study of factors that influence populations. Computers will now permit at short notice a tabulation of complex statistical data which might previously require years of clerical work.

Measurement in Medicine

According to Western historians, Celsus, two thousand years ago introduced measurement in medicine, which Hippocrates had considered impossible. In his description of anasarca (swelling all over the body), Celsus states: "It is good to measure every day with a string the circumference of the abdomen, and to put a mark where it surrounds the belly, then the day following, to see if the body is fatter or thinner".

"Nor is it unserviceable to take the measure of the drink and of his urine".

This may be considered the first reference to the intake—output chart so important in modern patient care.

Sanctorius (1561-1636) was the founder of the iatro-physical school, which attempted to treat the human body as if it were basically a machine. Some of these early attempts to blend physics with medicine were eventually successful. Sanctorius introduced the method of continuously weighing his patients over a period of days so that their input and output might be accurately recorded. He wrote in 1614; "If a physician who has the care of another's health, is acquainted only with sensible supplies and evacuations and knows nothing of the waste that is daily made by insensible perspiration, he will only deceive his patient and never cure him". The method of estimating metabolic balance has value in assessing day to day changes in acutely ill patients with rapid fluid changes. Yet it is only in the last two decades that a metabolic bed built on the principles of Sanctorius has been in use for purposes of medical research and more recently in renal dialysis units.

Measurement of Blood Pressure

In 1733, Stephen Hales made the first logical advance on Harvey's discovery of the mechanical nature of circulation of blood, when he measured arterial blood pressure. He inserted into the crural artery of a mare a brass pipe of bore 1/6 inch diameter, connected to a glass tube 9 feet in length, and measured the column of blood in the glass tube. In 1807 Thomas Young devised a kymograph to record the measurements made permanently. In 1828 Poiseulle improved on Hales' technique by substituting for the 9-foot long glass tube a

mercury manometer, inserted into the artery through a lead cannula filled with potassium carbonate to prevent the blood from clotting. He called it haemodynamometer. In 1847, Ludwig, that ever-ingenious physiologist added a floater and a kymograph and turned it into a recording instrument. In 1855, Karl Vierordt attempted to measure blood pressure clinically by determining the weight necessary to obliterate the radial pulse at the wrist. In 1881 Ritter Von Basch improved on this method by obliterating the radial pulse by a water-filled rubber cushion attached to a manometer. Later he used an aneroid barometer. Potain introduced air instead of water, into an arm-band attached to aneroid barometer. The blood pressure apparatus familiar to all of us was introduced by Riva Rocci in 1896.

In the last five years, a portable ambulatory device for recording of sequential indirect arterial blood pressure and continuous electrocardiogram has become available. The device is useful in the evaluation of labile or borderline hypertension, drug therapy programmes and syncopeal attacks.

Cardiac catheterization had been tried as early as 1860 on horses by Chauvean and Marey. It was a matter of general surprise to those who watched that experiment that the horses continued to munch their hay in an unconcerned manner while the pressure records were being taken. This might have been taken as a hint for its applicability to human beings, but the era of bacteriology was beginning and venipuncture became taboo for fear of infection.

In 1929 Forssman, anxious to avoid direct intra-cardiac injection through the chest wall, in emergencies, thought of making such injections through a catheter directed along a vein into the cardiac chambers. He passed one catheter into his own arm vein; he too was surprised at his own sense of well-being as he saw on the X-ray screen the catheter in his right ventricle. From this stage the advance to clinical applications depended on electronic amplifications and recording of signals picked up by pressure transducers. Right and left heart catheterizations have now become routine and provide a wealth of important information regarding pressures, flows and oxygen saturation of blood in various heart chambers and great vessels.

Ayurvedic Anthropometry

In *Charak Samhita* and *Sushruta Samhita* one finds a most fascinating section on anthropometry—the measurement of the various body segments and their proportions. The height, length and breadth of the

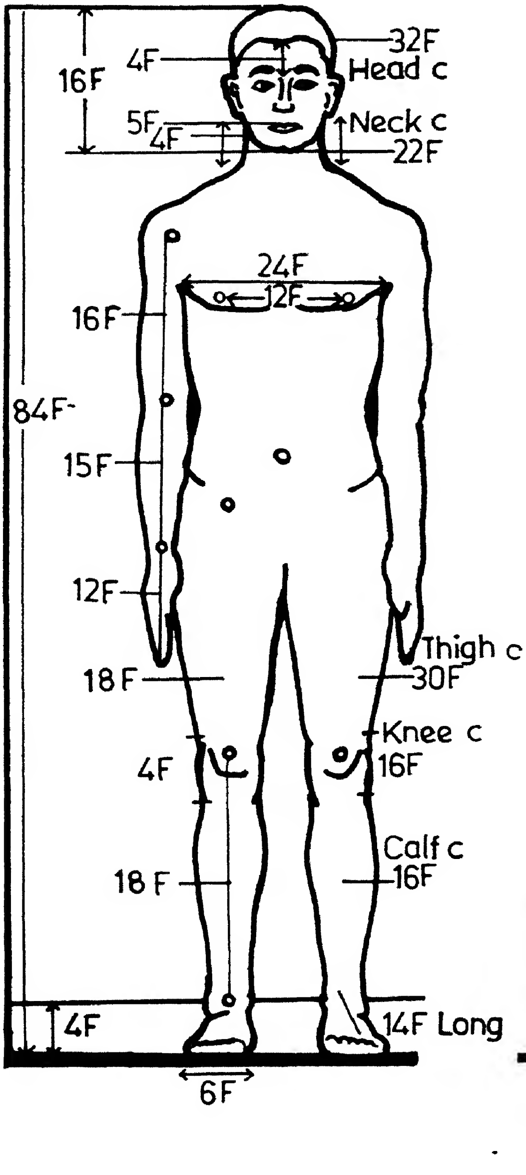
various limbs are measured in terms of the person's own finger-breadth.

"The feet are four fingers high, six fingers broad and fourteen fingers long. The calves are eighteen fingers long and sixteen fingers in circumference. The knees are four fingers long and sixteen fingers in circumference. The thighs are thirty fingers in circumference and eighteen fingers long. The testes are six fingers long and eight fingers in circumference. The phallus is six fingers long and five fingers in circumference. The vagina is twelve fingers in circumference. The waist region is sixteen fingers broad, the top of the pelvis is ten fingers, the stomach is ten fingers broad and twelve fingers long. The distance between the nipples is twelve fingers and their circumference is two fingers. The chest is twenty-four fingers broad and twelve fingers deep. The cardiac region is two fingers, the shoulders are eight fingers each, the shoulder blades are six fingers each, the rear arms are sixteen fingers each, and the forearms are fifteen fingers each, the hands are twelve fingers each, the axilla are eight fingers each, the sacrum ('trika') is twelve fingers high, the back is eighteen fingers high, the neck is four fingers high and twenty-two fingers in circumference; the mouth is five fingers broad; the chin, lips, ears, the nose and the forehead, the distance between the eyes are four fingers each; the head is sixteen fingers high and thirty-two fingers in circumference.

"The full length of the body is eighty-four fingers, and the breadth which is the full length of the outspread of the arms, is of the same length. Such proportion of the body is the proper proportion. Long life, strength, vitality, happiness, power, wealth and other desirable qualities are dependent on the proper proportions of the body. The contrary qualities characterise the body that falls short of or exceeds these proportions".

In another place, it is stated that "the very short or the very tall, the very corpulent or the very thin, the very hairy or the hairless, and the very dark or the very fair, are physiques that are censurable".

For comparison, I have given data published by the U.S. Department of Commerce, in "Annotated Bibliography of Applied Physical Anthropology in Human Engineering" wherein length of body segments is expressed as percentages of body height to simplify computations for many problems in biomechanics. The similarity between the two sets of data is indeed amazing *(Fig. 5.1 a* and *b).*



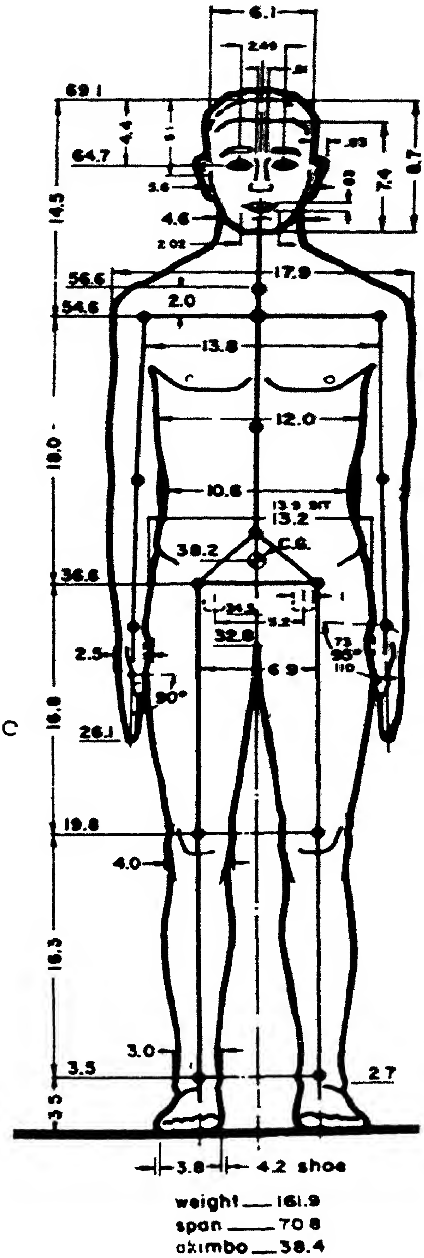


Fig 5.1a Ayurvedic Anthoropometry—
F = Finger breadth, C = Circumference.

Fig 5.1b Modern Anthoropometry

The Measure of Body Elements

Charaka describes various substances in the body which are measured in "Anjali" (a measure formed by joining both hands in the manner of a cup). "The measures here laid down relate to the ideal standard. These measures accordingly admit of increase and decrease; these too are to be only inferred. Thus, the measure of the aqueous elements in the body is ten anjalis measured with one's own hands. There are nine anjalis of the first metabolic product of the ingested food which is spoken of as the body nutrient fluid. There are eight anjalis of the blood, seven of the fecal matter, six of mucous secretion; five of bile; four of urine; three of the flesh-marrow; two of fat; one of the bone marrow; half an anjali of cerebro-spinal fluid; the same measure of seminal fluid and the same measure also of the vital essence".

We have come a long way in the measurement of body elements as exemplified by the 1983 edition of the world-renowned Harrison's 'Text Book of Medicine', which lists 360 items.

Concept of Measurement of Diet

In *Charaka Samhita,* while discussing diet, it is stressed that "one must eat in measure, and the measure of food is determined by the strength of one's gastric fire".

"Measured diet not only does not impair one's health but positively promotes one's strength, complexion, health and life".

It took science several centuries before measurement of energy derived from food became possible. Just before the French Revolution Lavoisier and the physicist Laplace carried out experiments in which they placed a guinea-pig in a very small closed chamber surrounded by ice. They measured the amount of ice melted over a 10 hours period and at the same time the amount of carbon dioxide given out by the animal. They demonstrated that there was a relationship between the heat produced by the animal and the respiratory exchange. Lavoisier also measured the oxygen consumption of men, and showed that it increased after food and exercise. For over a hundred years after his death on the guillotine, ingenious and learned men exercised their talents in designing *Calorimeters* to measure energy exchanges in man. Atwater, an American trained by Voit in Munich, enlisted the help of an engineer Rosa in 1892 to construct a human Calorimeter which could measure the heat produced by man with an accuracy of 0.1 per cent.

The energy content of food stuffs was measured by placing them in a

small chamber or bomb and exposed to a high pressure of oxygen in the presence of a platinum catalyst, and igniting it by a small electric current. All the organic material is burnt and the heat liberated can be measured. The available energy of proteins, carbohydrates, fats and alcohol was calculated by Atwater; he in 1894 concluded that 92% of protein, 95% of fat and 99% of carbohydrate and 100% of alcohol were normally absorbed, giving 17 kilojoules or 4 kilocalories per gm for proteins and carbohydrates, 37 kilojoules or 9 kilocalories per gm of fat and 29 kilojoules or 7 kilocalories per gm of ethyl alcohol. The energy values for foods given in tables of food composition are now routinely used by dieticians. The energy requirements of men, women & children have been worked out and Expert bodies have indicated "the proper measure"—of proteins and essential nutrients (vitamins and minerals) needed for maintenance of health.

Importance of proper dosage of drugs

Measurement was of paramount importance in drug therapy. Charaka states:" All treatment depends upon dosage".

"There can be no compounding of drugs without taking into account their measure of dosage".

"An underdose of medication cannot cure the disease just as a small quantity of water cannot quench a great fire. And medicine given in overdose will prove harmful just as excessive watering harms the crops. So, after carefully considering the severity of the disease and the strength of the medication, the physician should administer the medicine, neither in too large a dose nor in too small a dose".

"The dosage of medicines is dependent upon individual patient".

The Ayurvedic units of measurement of drug dosage were in terms of "gunja", "masa", "tola" for weight (*Kalpasthana. 12,* 87-97).

Measurement of Time

The ancient Indians had ingenious methods of measuring time and had devised different arbitrary units.

"Akshi nimish"	=	time taken for moving the eyelid or in articulating short vowels such as A.
15 akshi nimish	=	1 *"kashtha"*
30 Kashthas	=	1 *"muhurta"*
30 muhurtas	=	1 *"Din"* or day
15 Dinas	=	1 *"paksha"* or fortnight

2 pakshas	=	1 *"Masa"* or month
12 masas	=	1 *"Varsha"* or Samvatsara, or year

In relation to medicine, pulse was counted and described as slow or fast or irregular but the great difficulty through the ages was in finding suitable instruments for measuring short periods of time. In 1657, Huygens produced an accurate pendulum clock. Sanctorius (1561-1636) devised a *pulsimeter* to count pulse rate by the length of the pendulum measured against an accompanying scale. The earliest record of pulse rate comes from Galileo's fellow-astronomer Kepler who in 1604 counted the pulse rate believing it to be related to the Copernican cosmic system so as to beat 60 times to the minute. "Thus there should be in one minute sixty pulsations, but this slowness is rare, commonly seventy may be counted". But nobody could see the point in adopting pulse counting in clinical medicine, not even Harvey, the discoverer of circulation. In 1707 Sir John Floyer made an effort to introduce the practice of counting the pulse; in a work entitled the "Physicians' pulse watch", he wrote: "All I pretend is the discovery of a rule whereby we may know the natural pulse and the excesses and defects from this in disease".

In modern times many time-related physiological events are measured in clinical medicine, such as the various electrocardiographic intervals (PR, QT) and electro-mechanical cardiac intervals such as systolic time intervals, measured in milliseconds. In modern neurology, nerve conduction and sensory-evoked potentials (visual, auditory) are also measured in milliseconds.

The modern digital computers work at mind-boggling speed. The computers can store and recall information far more effectively than man's memory and can process the information with incredible speed and accuracy. Present day computer-assisted tomography has become possible only because of new concepts and developments in computer science and applied mathematics. For instance, in X-ray CT scanning, the absorption data within a single cross-sectional plane is acquired, and stored, on which the computer calculates approximately 90,000 X-ray attenuation measurements and then mathematically reconstructs an image within a second, because it can perform billions of mathematical operations per second.

Measurement of Mental Health & Mental Abilities

Tests and other devices for *measuring human abilities* are the province of

the psychometrician. He developes new tests, evaluates existing tests, and works to develop and improve statistical techniques used in measuring human abilities.

Attempts to measure intelligence culminated in 1916 in the first fully standardized test of intelligence, (the Stanford Binet test). Since then thousands of tests of many kinds have been used for all sorts of purposes with millions of people. While the single IQ test furnished by the Stanford-Binet is all that is needed to make predictions about ability to do school work in lower grades, the Wechsler Adult Intelligence Scale is more useful for adults. For personality assessment the MMPI (Minnesota Multiphasic Personality Inventory) is a practical tool. The MMPI scales have been useful in evaluating anxiety, hostility, hallucinations, phobias and suicidal impulses. In recent years it has been discovered that computers are capable of arriving at better MMPI assessments than the clinicians.

Mental health is difficult enough to define, and still more difficult to measure. Some indicators of the mental well-being or otherwise of society are illegitimate birth rates, divorce and separation rates, suicide, delinquency and crime rates, the frequency of rape, chronic alcoholism and convictions for drunkenness, prostitution and venereal disease.

Morbidity studies in general practice indicate that each year about 5 out of every 100 consult their family doctors because of some psychiatric disorder. Surveys of whole communities have given rather contradictory results because of differences in definition of mental, psychoneurotic and personality disorders. Depending upon criteria used to define mental illness, its prevalence lies somewhere between 1 in 20 and 1 in 5 in the general population.

Probability Theory & Statistics

Statistics is the mathematical technique or process of gathering, describing, organizing, analyzing and interpreting numerical data.

Because the field of statistics has become extremely important in medicine, it is desirable for every one to become acquainted with the language of statistics, the elementary concepts and a few of the more commonly used procedures.

Medical studies can be classified into two broad categories. *Descriptive studies* are intended to describe the characteristics of only the study group, using observations obtained from every member of the group. *Inferential studies*, on the other hand, are designed to enable the

investigator to use observations from selected individuals (a sample) to *make generalisations* or conclusions about the larger group (population) from which they were drawn.

For those who are unaccustomed tō mathematical thinking, mathematical and logical arguments, especially mathematical derivations and mathematical formulae can be uninviting reading material.

One characteristic feature of biological data is the *variability.* Information about variability is given by the range, the mean and the median values, and by quoting appropriate percentiles. Graphic display of data gives a quick visual impression of single continuous variables or the relationship between two continuous variables. When data are strongly skewed, the display sometimes can be made more convenient by a suitable transformation, such as taking logarithms of the original measurements. The same can be accomplished simply by plotting the original values on semilog paper. Generally transformations are more useful in inferential than in descriptive statistics.

In judging how accurately a sample mean estimates the population mean, one begins with the realization that large samples are more reliable representatives than small ones. The standard deviation has its greatest usefulness in relating sample means to population means – which is done by converting it to the standard error: —

$$\left(SE\bar{X} = \frac{S}{\sqrt{N}} \right)$$

Statistical Evaluation of Measurements

In interpreting the significance of a laboratory measurement, it is often helpful to know how the value obtained in a given case relates to a set of values from a healthy reference population. For this purpose we must find the distribution of the variable in the healthy population. Normal values of many variables are affected by age and sex. Statistical methods are available for estimating age and sex-specific percentiles.

In assessing the effectiveness of a particular drug in treatment, let us say, of high diastolic blood pressure, the question asked is: what is the probability of obtaining the observed difference between drug (E) and placebo (C) *by chance alone?* We compare the mean difference between groups to the variability present in both groups, using the t test.

$$t = \frac{\bar{E} - C}{\text{Spooled} \; \frac{1}{nE} + \frac{1}{nC}}$$

The denominator is the standard error of the difference in the numerator; we are computing a relative deviate dividing the numerator by its standard error.

By reference to suitable statistical tables, we find that the value of t (say 4.17) as large as that would be obtained by mere chance 1.8 times out of 100 ($P = 0.018$). Thus the data are not consistent with the null hypothesis (no drug effect) at $P = 0.018$. The observed result is so unlikely to occur without a real underlying difference that there almost certainly is such a difference.

When a drug is found to be efficacious in reducing diastolic blood pressure, we wish to know, for instance, the influence of the initial diastolic pressure on the reduction achieved by the drug. The first step in analysis is to exhibit the data graphically, relating the changes to initial values by use of a scatter diagram. In order to quantify and summarize the association shown by the scatter diagram we draw a straight line through the group of points. How well the line fits the data is measured by the sum of the squared vertical distances of the individual points from the line. Thus the best fitting line is the one for which this sum of squares is least, and it is called the *least-square line.* In general terms the least-square line may be described by the equation:

$$Y = a + bx.$$

This is the linear regression equation; the feature of greatest interest is the slope, the amount of change in Y per unit of increase of x. Let us say the sample slope (b) is 0.4671. We compare it to its standard error (SEb) which is 0.0751, so the test statistic is $t = b/SEb = 0.4671/0.0751 = 6.220$. From suitable tables or computing equipment we find that if $B = 0$, then the probability of obtaining a value of t as large as 6.220 is less than 0.001 ($P < 0.001$). So we reject the null hypothesis $B = 0$ and conclude that the drug response does depend on initial blood pressure.

Instead of continuous variables like blood pressure, we may wish to compare dichotomous variables which are observed as yes—no, alive-dead, normal-abnormal, and so on. For instance let us compare the in cidence (yes—no) of a side effect (headache) in association with each of two drugs; 15 of 50 cases with drug F and 8 of 50 cases with drug G. The dichotomous observations of each group can be summarised by a proportion, which will express the incidence within that group as a degree on a continuous scale of possibilities. We can use the sample proportion $PF = 0.30 (15/50)$ and $PG = 0.16$ (8/50). We then ask the familiar question – is there a real difference between those groups – that is, does $F = G$? If so, how large may the difference be?

If F = G, we can write this unknown common proportion as < 0. To obtain a corresponding sample statistic (PO) in accord with the null hypothesis that there is no underlying difference between the samples (that the apparent difference is only random variation) we pool the samples $PO = \frac{15+8}{50+50} = 0.23$

Again we compute the ratio (here we use the test statistic 2) of the difference between the two data to the standard error of the difference:

$$Z = \frac{PF - PG}{PO(1 = PO)\left(\frac{1}{nF} + \frac{1}{nG}\right)} = \frac{0.30 - 0.16}{0.23\ (0.77)\left(\frac{1}{50} + \frac{1}{50}\right)} = 1.663$$

Here we are asking, "is either F or G superior to the other?" Hence, we look for the probability of getting a value of Z that is either 1.663 or higher (signifying more headaches with drug F) or − 1.663 or lower (signifying more headaches with drug G). From appropriate tables, this probability P = 0.096. So we remain unsure that either drug excels the other in regard to incidence of headache.

When we ask the question "Is experimental drug A superior to placebo?" we are looking for a difference in one direction. When we ask if either drug A is superior to drug B, we are interested in establishing superiority in either direction. The study objectives and specific hypothesis to be tested should be formulated before the data are collected. In practice, tests, for comparing two proportions are most commonly referred to as Chi-square tests (actually Z^2 in our example), denoted by the symbol X^2.

Evaluating a new diagnostic procedure's efficacy

When a new medical procedure has been developed such as CT scanning, it is necessary to evaluate the contribution to patient care that will result from its use. Three aspects that should be considered are the reliability of the procedure, its accuracy and its comparison with earlier methods. The statistical methods employed will differ slightly according to whether the measurement of interest is dichotomous (e.g. presence or absence of a tumour) or continuous (e.g. tumour size).

Reliability or precision of a method is its ability to provide the same answer in repeated observations.

Accuracy of a procedure is measured by its ability to give the right answer. Usually this is expressed by rates of false positives and false negatives, provided of course that there is some independent way of establishing the true status (surgery or autopsy). For reasonably accurate estimates a study of 100 cases might be considered as a minimum sample.

Survivorship Studies

How will a particular disease, or a particular form of therapy affect life expectancy? The methods for analyzing survival data have been developed more recently than the other statistical methods, and still newer techniques are being proposed continually. Procedures are available for testing the differences between two or more survival curves, for testing the association between survival and a continuous risk factor (such as serum cholesterol, smoking or high blood pressure).

Generally the most effective method for describing the survival experience of a group of patients is to graph survival rates against time. A comparison with normal survivorship may be shown.

Because survivorship studies generally are observational rather than experimental, questions arise regarding what has caused the differences that are found. For instance suppose that two different surgical techniques were used to treat patients having the same disease and that 10-year follow-up was obtained on all patients treated with each method. It would be tempting to attribute any difference in survivorship to the difference in surgical techniques. However, other factors might be operative as well, such as severity of illness, age of the patient. In order to establish the relative merits of the two techniques it would be best to design an experiment specifically with this purpose in mind, assigning age-and-sex matched subjects randomly to each group.

An important principle is that statistics can only establish an association and cannot define the cause and effect.

Probability Theory & Medical Decisions

In 1968 Dr. Henry Wagner proposed a model of the entire diagn

process based on the sequential application of Bayes' Theorem of Conditional Probability. He emphasised that medical diagnosis was probabilistic in nature and hence eminently suited for applying probability theory. "Every question that the physician asks in obtaining a medical history, every manoeuvre that he performs in the physical examination, and every subsequent laboratory procedure that he orders, should be selected because of the likelihood that the new fact will alter the estimate of probability that the patient has a particular disease or diseases. With the availability of mini-computers, Bayes' theorem seems to be an idea whose time has come".

The essence of Bayes' Theorem is:

$$P(Di/Sj) = \frac{P(Sj/Di) \times P(Di)}{\Sigma i[(P(Sj/Di) \times P(Di)]}$$

This equation states that the probability (P) that a patient with a given syndrome (Sj) has a particular disease (Di) is directly proportional to the probability of occurrence of his syndrome in that disease P(Sj/Di) multiplied by the *a priori* prevalence of that disease P(Di), and inversely proportional to the probability of occurrence of his syndrome in all diseases times the prevalence of those diseases.

In the application of Bayes' theorem the term P(Di) refers initially to the prevalence of that disease in that particular community from which the patient comes forward with a given problem or problems, and enters the diagnostic process. Thereafter the *a priori* diagnosis at each stage becomes the *a posteriori* diagnosis after each stage is completed. The physician waits to make a therapeutic decision until there is sufficient certainty to warrant a decision. At any stage of the process he may take a therapeutic decision or defer until more information is obtained. Rifkin and Hood in 1975 evaluated a Baysean approach to the interpretation of exercise ECG testing. They found that the predictive value of a quantitative analysis of the degree of exercise-induced ST segment depression using a Baysean approach, was quite high in diagnosing coronary artery disease as evidenced by coronary angiography. Now computer programmes are commercially available for the diagnosis of coronary artery disease.

Cluster Analysis

The notion of an n-dimensional space is commonly used in applied mathematics. The complete state of a patient may be represented by a

set of n events (which include continuous variables like plasma cholesterol, and discrete variables like sex). A large number of persons, randomly selected, may each be represented by a point in the event space. Such points may fall into *Clusters,* some of which correspond to disease entities. Cluster Analysis is of value whenever there is need to define classes. Numerical taxonomy is a new mathematical tool which measures similarity coefficients. Much of the mathematics of Cluster Analysis is new and still developing. The main application of Cluster Analysis is likely to be in the formal representation of a specific disease for the purpose of diagnosis, and also to discover disease classes as yet unrecognized. If diseases can be represented by Clusters in some space, then it should be possible to get a measure of the distance between the Clusters. The smaller the distance, the greater the difficulty the doctor faces in distinguishing the diseases.

Expected Utility & Principle of Rationality

To develop a logical analysis of medicine it is necessary to assume that it is possible to attach a measure of worth or value to any state of health. The word for this measure is *utility,* used in a sense borrowed from economists. A doctor attempts to increase each patient's utility, but has no certainty, only a probability of achieving this. Hence it is more accurate to speak of expected utility and a doctor's objective as the *maximization* of *expected utility.*

The objective can be achieved only after performing a series of diagnostic tests, which may be elaborate, tedious or even painful, and after some form of treatment. Each diagnostic test and each form of treatment involves a *cost,* or negative contribution to utility. A cost may be expressed in financial terms or in terms of danger or risk to life, anxiety or pain. All those costs have continually to be included as negative utilities, in estimating the expected gain in utility.

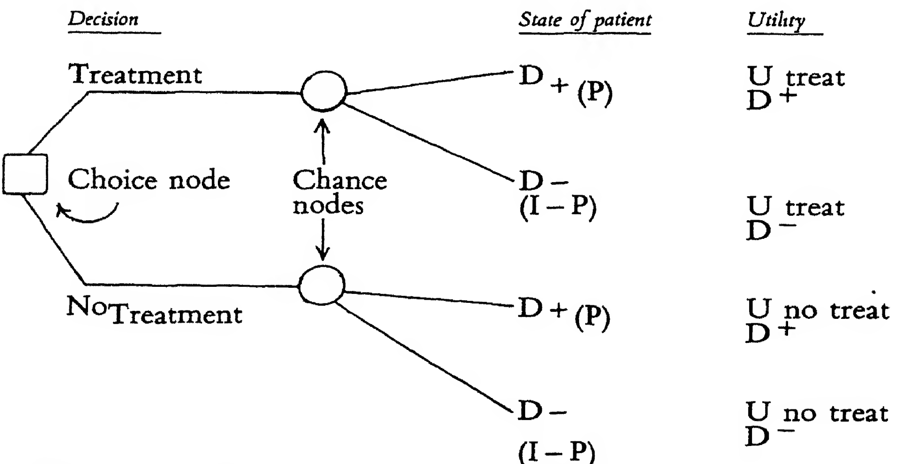
Entropy is a concept of classical thermodynamics which is now being applied to other sciences. Entropy is related to the degree of disorder or randomness, and in relation to medical decision-making, could be replaced by "uncertainty". Hence a basis for rationality in medical decision-making is the maximization of expected utility and minimization of expected entropy. The maximization of expected utility, by choice of actions, is known as the principle of rationality.

To make a prediction about a specific patient (prognosis) on giving a specific treatment (or null treatment) a *linear discriminant function* is used. It may be possible in future to automate medical decisions, but it

will be safe to say that the human brain with its astonishing power of pattern recognition, will continue to make complicated decisions so frequently needed in medicine.

Decision Analysis

Therapeutic decision-making under conditions of uncertainty can be done in an explicit and logical fashion. This approach includes construction of a decision tree that describes the possible courses of action available and the consequences of each; obtaining a *quantitative estimate* of the probability and utility (value) of each outcome; and combining the estimates by a method that provides a measure of the "expected value" or worth of each course of action. Starting from these principles, a simple and clinically useful mathematical relation has been derived between the *benefits* and *costs of a treatment* in a given disease and the *threshold level* of clinical suspicion of the disease. When the probability of a patient's illness exceeds this threshold level, the better choice is to administer treatment; when the probability is below the threshold, the better choice is to withhold treatment. The method is applicable to many problems that physicians encounter in a variety of medical disciplines and is useful in clinical situations even when an exact assessment of the benefits, cost and the probability of disease cannot be made. Computers have greatly facilitated decision analysis.



Ideally one would choose to treat only patients with the disease and avoid treating those without the disease.

Net benefit (B) = U treat D_+ U no Treat D+
Net cost (C) = U no treat D_- − U treat D−
Benefit represents the net benefit of appropriate therapy and cost represents the net cost of unnecessary.

$$T = \frac{C}{B+C} = \frac{1}{\frac{B}{C}+1}$$

Example – Suspected acute appendicitis

Assumptions made:

1) Operative mortality of laparotomy 0.1 per cent; survival with surgery is thus 99.9 per cent.

2) Mortality of app. with perforation is 4 per cent: 50% probability of perforation if op. delayed and mortality of 2% for perforation. Thus overall mortality is 1% for deferring necessary operation and survival for this coleost without immediate operation is 99%.

Calculations:

Benefit (B) = 99.9% − 99% = 0.9%
Cost (C) = 100% − 99% = 1.0%
B/C = 9

$$\text{Threshold } T = \frac{1}{\frac{B}{C}+1} = \frac{1}{9+1} = 0.1$$

Computer-intensive methods in statistics

Most statistical methods in common use today were developed between 1800 and 1930, when computation was slow and expensive. Now computation is fast and cheap. In the past few years there has been a surge in the development of new statistical theories and methods that take advantage of the high-speed digital computer. The new methods are fantastic computational spend-thrifts; they can easily expend a million arithmetic operations on the analysis of 15 data points.The pay-off for such intensive computation is freedom from two limiting factors that have dominated statistical theory since its beginning.

The assumption that the data conform to a bell-shaped curve and the need to focus on statistical measures whose theoretical properties can be analysed mathematically.

These developments have profound implications throughout science, because statistical theory addresses a grand question: how is one to learn what is true? What is the best estimate of the true value? In older methods it was generally necessary to make certain unverifiable assumptions about the data before statistical analysis could proceed. The *Gaussian distribution* (after the German mathematician Carl Friedrich Gauss), depicted on a bell-shaped curve, assumes that random fluctuations, or errors in the experimentally observed values of some quantity are scattered symmetrically about the true value of the quantity. Computer-intensive methods can solve most problems without assuming that the data have a Gaussian distribution.

Freedom from the reliance on Gaussian assumptions is a signal development in statistics, but the second advantage of the new technique is even more liberating. Many other properties of a statistical sample other than the mean, the standard deviation and the correlation coefficient, are of interest to the statistician but are beyond the reach of exact mathematical analysis. The new computer-based methods make it possible to explore such properties numerically, even though their exact analysis is currently impossible. A method called *bootstrap,* invented by Bradley Efron, professor of Statistics at Stanford University, is applied to assess the accuracy of correlation coefficients (r), which is a measure of the tendency of data points plotted on a graph, to cluster about a line; the more linear the clustering, the greater the absolute value of (r). The name 'bootstrap', which is derived from the old saying about pulling yourself up by your own bootstraps, reflects the fact that one available sample gives rise to many others. The samples generated in this way are called bootstrap samples. The calculation of a single correlation coefficient with a desk calculator takes about five minutes. Today calculation on 1000 bootstrap samples takes less than a second and costs less than a dollar.

Several other methods such as the jack knife, cross-validation and balanced repeated replications are similar in spirit to the 'bootstrap' but quite different in detail. Each of these procedures generates fake data sets from the original data and assess the actual variability of a statistic from its variability over all the sets of fake data. Sir Ronald Fisher was able to provide a statistical theory that took full advantage of the computational facilities of the 1920's. The goal now is to do the same for the 1980's.

Chapter 6

PHYSICS AND MEDICINE

Introduction

The union of modern biology with physics and chemistry is an outstanding development of twentieth century science. Physical and chemical approaches to problems in biology have become increasingly productive in recent years. Major advances in the understanding of life processes have been made through research in specialities such as biophysical chemistry, molecular biology, biophysics and electrophysiology. Attempts to understand living processes in terms of the laws of physics and chemistry have been significantly fruitful and will surely continue.

In the 1930's the eminent physicist Niels Bohr speculated about the relevance of Heisenberg's uncertainty principle and the concept of complementarity to biological research. Bohr's speculation was further elaborated by Max Delbruck, whose idea about the physical nature of the gene led Erwin Schrodinger to write a small book entitled "What is life?", in which Schrodinger treated the gene not as an abstract unit but as concrete physical substance, advancing definite hypotheses about its molecular structure that stimulated scientists to think about genetics in a new way. A crucial element in the breaking of the genetic code was the fact that physicists moved into biology. The confluence of three powerful methods of observation – chemical analysis, electron microscopy and X-ray crystallography, enabled scientists like Maurice Wilkins and Rosalind Franklin to generate data which helped James Watson and Francis Crick to determine the precise architecture of DNA as a double helix made up of two intertwined, structurally complementary chains.

While there are innumerable examples of the impact of physics on biology, one can think of at least one example of the impact of biology on physics. Luigi Galvani, at the end of the 18th century,

demonstrated that the transmission of nerve impulse in a frog was associated with an electric current. This observation led Alessandro Volta to the study of electricity and thus became the source of two new sciences, neurophysiology and electrodynamics.

The most fascinating recent applications of physics to biology and medicine are in the fields of nuclear medicine and nuclear magnetic resonance (NMR). These will be discussed in some detail later on in this chapter.

Mechanism of Vision

The idea that the human body is a mechanism was first successfully exploited in the experimental and theoretical inquiries made during the 17th century into the mechanisms of the sense organs, particularly the eye and the ear.

Johannes Kepler in 1604, provided the basis of the modern understanding of vision. The pre-Kepler theory was that of the Arab philosopher Ibn Al-Haitham, better known by the Latin version in the West, Alhazen. Following the theories of his predecessors, particularly Euclid, Galen and Ptolemy, Alhazen supposed that a "visual cone" of rays extended from the object to the eye and that the lens was the sensitive organ. He then proposed the original theory that the image of the object was propagated by physical rays sent from each point on the object to a corresponding point on the sensitive forward surface of the lens, which thus brought about a perception of the whole object through the separate perceptions of each of its points. Alhazen also described an experiment with a camera obscura in which, "when a number of candles were set up outside an opening leading into a dark place, with an opaque wall or body opposite the opening, the images of these candles appeared on the body or wall, each distinctly." Alhazen's difficulty was that he knew that in an optical system such as the eye the image would be inverted unless some refraction occurred. So, in order to preserve the erect image that he thought was necessary for the eye to cause us to see as we do, Alhazen postulated that the rays would be refracted at the back of the lens in such a way that they did not intersect. The two erect images formed at corresponding points in each of the eyes then united at the junction of the two optic nerves to form a single image that was conveyed by the "visual spirit" sent out from the brain to the "ultimate seat of sensation" in the cerebral cavity, the location of the "common sensory".

It was a stroke of genius for Alhazen to impose geometrical optics on anatomy. His difficulties arose because he was not resolute enough.

Kepler's new concept was based on a complete willingness to exploit the mechanistic hypothesis, while earlier, several brilliant attempts to explain vision failed for want of complete commitment to the mechanistic approach. Leonardo da Vinci compared the eye to a camera obscura and introduced an engineering approach to the problem of vision with a proposal to investigate it by means of models using glass balls, but like Alhazen and for the same reason, he found it necessary to arrange the optics to suit the demand for an erect image.

Felix Plater in 1583 put forward the fundamental idea that the retina and not the lens is the sensitive organ of vision. Kepler approached the optical problem by showing that the formation of the image in the eye must be analysed geometrically not as a cone of rays extending from a base on the object to a vertex in the eye but in terms of a multitude of cones coming from vertexes at every point in the object to a common base on the lens. He described the physical process of vision thus: "vision is brought about by a picture of the thing seen being formed on the concave surface of the retina. That which is to the right outside is depicted on the left of the retina, that to the left on the right, that above below and that below above."

The psychophysiological question of how the physical processes of the eye effect sensation lay outside Kepler's mathematical solution. "I leave it to the natural philosophers," he said. By asking questions that were answerable because they involved physical and mathematical analysis rather than philosophical speculation, Kepler opened the way to the solution of further problems of vision by purely physiological methods. Further progress became possible because of progress in physical optics and in electrophysiology achieved by people like Helmholtz.

One of the first great insights about perception of vision came late in the 19th Century from clinical, physiological and anatomical sources. It was noted that a brain injury, depending on its location, could cause paralysis or blindness or numbness or speech loss; the blindness could be total or limited to half or less of the visual world. The consistency of the relation between a given defect and the location of the lesion gradually led to a charting of the most obvious of these specialized regions, the visual, the auditory, somatic sensory, speech and motor regions. Additional confirmation came from observations of the location (at the surface of the brain) of the electrical brain waves produced when an animal was stimulated by touching the body, sounding clicks or tones in the ear or flashing light in the eye.

The systematic mapping of the cortex of the brain soon led to a fundamental realization; most of the sensory and motor areas contained systematic two-dimensional maps of the world they represented. The visual world was mapped on to the primary visual cortex, an area on the occipital lobe that in man covers about 15 square centimetres. The left half is projected to the right cerebral cortex and the right half projected to the left cortex.

The visual pathway from the retina to the primary visual cortex has been fully worked out. In recent years ingenious methods of axonal transport using radioactive tracers have been used, like injecting radioactively labelled amino-acids into an eye of a monkey. The retinal ganglion cells take it up and transport it along their axons, the optic nerve fibres; the destination of these fibres in the lateral geniculate ganglion is studied by radio-autography. After a large enough injection in the eye, some tracer is taken up by cells in the geniculate and transported along their axons to the cortex. Another method is the use of radioactive deoxyglucose which reveals active areas where cells will have taken up more deoxyglucose than those in quiescent areas. By applying the two methods, axonal transport and de-oxy glucose, Hubel and his colleagues have been able to demonstrate an elementary unit of the primary visual cortex as a block about a millimetre square and two millimetres deep. It contains one set of orientation slabs subserving all orientations, and one set of ocular dominance slabs subserving both eyes. The pattern is reiterated throughout the primary visual area.

There was a time, not so long ago, when one looked at the millions of neurons in the various layers of the cortex and wondered if anyone would ever have an idea of their function.

For the visual cortex the answer seems to be known in broad outline: particular stimuli turn neurons on or off; groups of neurons do indeed perform particular transformations. If the secrets of a few regions such as the visual cortex can be unlocked, other regions will also in time give up their secrets. Neurobiologists are still far from knowing how objects are perceived or recognized. Yet the amount that has been learned in the few years since microelectrodes became available does suggest that a part of the brain such as the cerebral cortex is, at least in principle, capable of eventually being understood in relatively simple terms.

Vision and Light

In 1874 J. H. Van't Hoff proposed the notion that molecules of the

same chemical composition might have different molecular architecture. The eminent organic chemists of the day dismissed this idea as "childish fantasy". In 1900 Van't Hoff was named the first recipient of the Nobel Prize in chemistry for his idea of steriochemistry, which has great relevance to our understanding of vision.

The idea of steriochemistry can be illustrated by two simple compounds, maleic and fumaric acids, two distinct, chemically pure substances, each with the same formula $C_4H_4O_4$. The form of $C_4H_4O_4$ in which the two terminal COOH groups lie on the same side of the double bond (maleic acid) is called the *"cis"* form (Latin for same side). The form of $C_4H_4O_4$ in which the COOH groups lie on opposite sides is called *"trans"* (Latin for opposite side). So maleic and fumaric acids are *Cis—trans* isomers of each other.

Franz Boll in 1877 noted that when a frog's retina was seen immediately after removal from the eye, it was bright red, but bleached as he watched it, becoming first yellow and finally colourless. Subsequently Boll observed that in a live frog the red colour of the retina could be bleached by a strong light, and would slowly return to red if the animal was put in a dark chamber. Boll named the pigment *"erythropsin"* or visual red. Before long Willy Kuhne of Heidelberg found the same red pigment in the retinal rod cells of many animals and renamed it *"rhodopsin"* or visual purple. In 1933 George Wald of Harvard University demonstrated that the eye contained vitamin A. In 1944 R. A. Morton of Liverpool showed that the yellow carotinoid retinene is formed when Vit. A, an alcohol, is converted to an aldehyde. In 1952 Ruth Hubbard showed that only the 11 *cis* isomer of retinene (now called retinal) can serve as the chromophore or colour bearer of rhodopsin. Light changes the shape of the molecule from a 11 *cis* to *all-trans* configuration, which triggers the nerve excitation. It is remarkable that *all* animal visual systems depend upon the photoisomerisation of retinal for light detection. In a dark-adapted human eye, seeing requires at least five quanta of light photons falling almost simultaneously within a small area of the retina.

Electrical Activity of the Heart

An eventful discovery in 1882 by the English physiologist Sydney Ringer was that a solution containing salts of sodium, potassium and calcium and a little alkali, in the concentrations found in the blood, would sustain the beat of an excised frog's heart. Later it was found

that the addition of glucose or lactic acid would extend the heart's performance.

During the present century the scientific minds have sought to learn how these inorganic elements are involved in the initiation and spread of impulses. When a salt is dissolved in water, the elements are dissociated and become ions charged with positive and negative electricity.

The delicate enclosing membrane of all cells is differentially permeable, that is, ordinarily it allows potassium ions to enter the cells but excludes sodium ions. The net result is that the outside is more positive than the inside, and the interior can therefore be regarded as negative with respect to the exterior. The potential difference is about one tenth of a volt or hundred millivolts. Each cell thus becomes a small charged battery.

A barely visible knot of tissue in the rear wall of the right atrium of the heart, called the sino-atrial or S-A node liberates a brief electrical spark of low intensity seventytwo times every minute. Now, in the case of the cells of the S-A node, the cell membrane leaks slightly, allowing some sodium ions to sneak in. This slowly but steadily reduces the potential difference between the inside and the outside of the membrane. When the difference has diminished by a critical amount (usually 60 millivolts), the tiny pores of the membrane abruptly open, and a crowd of sodium ions rushes in, while some of the intracellular potassium escapes to the exterior. As a result, the relative charges on the two sides of the membrane are momentarily reversed, the inside being positive with respect to the outside. The action potential thus created is the release of the electrical spark.

As soon as the activity is over, the membrane repolarizes, i.e. reconstitutes a charged battery.

When the pace maker cells discharge, they generate a highly localised current which in turn causes depolarisation and discharge of an adjacent group of cells and thus the impulse is relayed to the muscle cells concerned with contraction.

The "membrane hypothesis" was first put forth in 1902 by Julius Bernstein in Germany. Bernstein suggested that the cell membrane's selective permeability to potassium might account for the resting potential. Experimental proof of the hypothesis came later with the availability of a proper experimental tool. The Giant nerve fibres of the squid, found in great numbers on both sides of the North Atlantic,

allowed physiologists to study the propagation of the nerve impulse experimentally. It was possible to push micropipettes 0.1 millimeter in outside diameter, two or three centimetres down the inside of the axon, carefully steering the tip to avoid scraping the membrane at any point. After the second world war another form of micropipette with a tip tapering to a point no more than 0.0005 millimeter across, was devised. This tool can be thrust through the membrane to reach the interior of the thin fibres that are found more commonly in nature than the giant axons of the squid. In most cells the resting potential lies between 50 and 100 millivolts, while at the peak of the spike the potential is reversed by 20 to 50 millivolts.

The cells must work constantly to maintain the high intracellular potassium, and pump sodium out in the surrounding fluid. Using radioactive isotopes evidence was obtained for *"sodium pumps"*. Dinitrophenol, a metabolic poison, brings the outward passage of labelled sodium to a halt. Parallel experiments which measure the movements of labelled potassium proved that metabolic inhibitors cut down the uptake of potassium and extrusion of sodium to roughly the same extent.

The use of specific neurotoxins as molecular probes has permitted scientists to define the density and distribution of voltage-sensitive sodium channels in neurons and to identify, purify and characterize the molecular components of sodium channels in neuron surface membranes. Most neurons have between 100—200 sodium pumps per square micrometre of membrane. Using energy derived from ATPase, each pump can transport across the membrane some 200 sodium ions and 130 potassium ions per second, to maintain trans-membrane gradient of Na & K, that enables neurons to propagate nerve impulse. Today's student of Ayurveda may well consider this as a modern version of the *"Vata"* concept.

Biological Transducers

Certain cells specialize in the reception of external stimuli. The rods and cones in the retina of the eyes respond to light. The thermal receptors in the skin respond to heat and cold. The mechano-receptors in muscle respond to mechanical stimuli such as pressure and stretching. The olfactory nerve cells and taste receptors on the tongue respond to chemicals. All of them act as biological transducers, which convert information from external stimuli into electrical signals.

The transducer mechanism in the mechano-receptor was first demonstrated in 1950 by Bernhard Katz of University College, London. He discovered that the stretching of a muscle spindle (a mechano-receptor built into the skeletal muscle) generates a local electric current called the generator current. When this current reaches a certain intensity, it triggers the firing of an impulse in the nerve fibre leading from the muscle spindle to the higher nerve centres.

Vertebrates possess mechano-receptors in all organs in which active or passive movements occur, including the digestive tract, the lungs, the heart and the blood vessels, as well as the skin and the skeletal muscles. These receptors feed into the nervous system information about movement, tension and pressure.

The receptor chain begins with a stimulus of a given energy content; the stimulus is transformed into a generator current with an energy current proportional to that of the stimulus, and the chain ends in a signal—the nerve impulse, with an energy content that bears no relationship to either of the preceding events. How can the all-or-none signal of the nerve impulse convey quantitative information about the strength of the stimulus along the nerve fibre? A clue is furnished by the fact that many man-made information systems operate with all-or-none signals. Digital computers send and store information by all-or-none pulses. Biological sensory systems operate on the same digital principle. *Frequency-modulated systems* translate an increase in the *intensity* of the stimulus into an increase in the *frequency* of the nerve impulse.

Physiologists deal with information systems in which signals are carried by ions through conduction lines composed chiefly of water and salts. We may picture the receptor as a membrane in which there are a number of tiny holes. In the resting state the holes are too small for certain ions to pass. Mechanical deformation of a given area opens (excites) a statistically determined number of holes, and the ions move through these, setting up the generator current. As the stimulus strength increases, an increasing number of holes opens up and a correspondingly increasing number of ions passes through the membrane.

The linear relationship between stimulus and response is characteristic of all sensory receptors and in all sensory circuits. The rise in the intensity of the generator current increases the frequency of the nerve impulses dispatched to the higher nerve centres.

The Electrical Activity of the Brain

In 1929 Hans Berger, a German psychiatrist published the first pictures

of the electrical activity of the human brain, but no one took them seriously. For several years no one even bothered to repeat his experiments. In the 1950's electro-encephalography found its useful role in the diagnosis and treatment of brain diseases. The complexity of the brain waves can be understood if we consider that there are 10^{11} neurons in the brain and probably 10^{15} synapses. There are 100,000 neurons per square millimetre of the cerebral cortical surface. The Electroencephalogram (EEG) is a *composite record* of the electrical activity of all those neurones.

Nevertheless, the normal EEG in adults is easy to recognize. It shows somewhat asymmetric 8-12 HZ, 50/μv sinusoidal *alpha waves* in both occipital and parietal regions. These waves wax and wane spontaneously and usually disappear promptly when the patients open their eyes or fix their attention on something. Faster waves than 13 HZ of lower amplitude ($10-20$ μv) called *beta waves,* are also seen symmetrically in the frontal regions. Very slow waves *(delta),* sharp waves or other unusual patterns are absent in a normal record. When normal subjects fall asleep, the rhythm slows symmetrically and characteristic wave forms (vertex sharp waves and sleep spindles) appear.

The most pathologic finding of all is the disappearance of the EEG pattern and its replacement by a flat record representing electrocerebral silence. In the absence of CNS depressants or extreme hypothermia, a flat record all over the brain is almost always a result of cerebral hypoxia or ischemia. Such a patient, without EEG activity, spontaneous respirations, reflexes or muscular activity of any kind for 6 hours or more, is said to be in "irreversible coma". The patient may be considered *dead,* despite the preservation of vegetative (cardiovascular) functions supported by mechanical means, such as respirators. The legal acceptance of "brain death" in a patient with a beating heart has facilitated human organ transplant programmes.

The EEG is useful in reaching a correct diagnosis in epilepsy, brain tumour, abscess and subdural haematoma. In unconscious patients where the pertinent history is not available, EEG may point to such otherwise unexpected causes as hepatic encephalopathy, intoxication with barbiturates, or benzodiazepines, large space occupying lesions or diffuse hypoxic-ischemia.

Evoked Responses

The usefulness of EEG has been enhanced by recording the electrical

activity produced by a group of neurons within the spinal cord, brain stem, thalamus, or cerebral hemispheres following stimulation of one or another sensory system by means of visual, auditory or tactile input. Because of their extremely small size, these potentials need special amplifying techniques for recording and the use of computers to extract the evoked response wave form from the continuous on-going background ECG activity. These techniques are called "averaging" because the process involves repeating 100 to 1000 precisely timed stimuli and recording the electrical activity during a certain brief interval following the stimulus.

Modern Brain Research

In the past decade neurobiology and brain research have become the most active branches in all science. The physical sciences have provided the necessary tools and techniques. In order to advance anatomical knowledge we need first the light microscope and then the electron microscope. Knowledge of neurophysiology required the microelectrode. Selective methods of staining nerve tissue invented in the early 1950's by W. J. H. Nauta, extended the earlier work of Golgi and Cajal. If a particular part of the brain is destroyed and the brain is stained by the Nauta method a few days later and examined under the microscope, the presence of selectively stained fibres in some second, and perhaps quite distant part, means that the second region receives fibres from the destroyed part. The method has led to an enormous expansion in detail of the map of the brain.

A new tool of investigation is transport auto-radiography. A radioactive chemical is injected into a brain structure; cell bodies take it up and transport it along their axons and it accumulates in the terminals. When a photographic emulsion is put in contact with a slice of brain tissue, microscopic examination of the exposed silver grains in the emulsion reveals the destination of the axons.

The latest in this series of advances is the deoxyglucose technique invented by Louis Sokoloff of the National Institute of Mental Health in U.S.A. Glucose is the fuel for neurons, and the cells consume more glucose when they are active than when they are at rest. Radioactively labelled deoxyglucose is taken up by the cells as if it were glucose. It is broken down like glucose but cannot be further metabolised; it also cannot escape from the cell hence it accumulates there, and the extent of radioactivity in particular cells shows how active they have been.

Very recently, positron-emission tomography (PET) has been developed that makes it possible to detect from outside the skull the presence of deoxyglucose or other substances labelled with positron-emitting radionuclides. This promising technique permits the mapping of the metabolic activity of the living human brain. For neurologic studies PET employs a wide variety of reliable, quantitative tracer kinetic studies to measure such diverse things as regional cerebral blood flow, blood volume, oxygen consumption, tissue pH, blood brain barrier permeability, tissue drug distribution and receptor pharmacology.

Various Forms of Energy

There are five forms of energy: chemical, electrical, mechanical, radiant and nuclear energy. All have relevance to biology and medicine in various ways.

Energy is constantly being changed from potential to kinetic and back again, The biological world is no exception. Living organisms operate by changing the potential energy found in foodstuffs into the kinetic energy of muscle contraction, protein synthesis, membrane transport etc. Life is completely dependent upon energy. *Chemical energy* is the most fundamental form of energy in the life processes.

Electrical energy is the result of the flow of electrons along a conductor. The movement of electrons is important in living organisms. Electrons play a major role in the energy changes within the living organisms. Our neuronal function and heart beat depend upon transmission of electrical signals together with chemical signals.

Solar energy is crucial for life on this planet. Sunlight provides the energy for *photosynthesis* by which green leaves of plants make organic molecules and which sustains life directly or indirectly. Approximately 50 per cent of the sun's radiant energy is in the visible portion of the spectrum (400 to 760 nanometers), about 40 percent in the infra-red region and about 10 per cent in the ultra-violet (UV) region. Our skin, eyes, blood vessels and certain endocrine functions respond to radiation from the electromagnetic spectrum of the sun. The formation of calciferol (vitamin D) from sterol precursors in the skin by solar UVR exposure has long been recognized in the management of rickets. Certain of our biorhythms are dependent on the cycle of sunlight.

Light, that form of radiant energy which is visible to the human eye, is only a narrow band in the whole spectrum of electromagnetic radiations, which consists of electric waves, radiowaves, infra-red rays, visible light, UVR, roentgen rays (X-rays), gamma rays and cosmic rays.

The heat produced by metabolism leaves the body by radiation (about 45 per cent), convection (30 per cent), evaporation (20 per cent) and conduction (5 per cent). At room temperature the main source of heat loss is radiation and this constitutes the basis for *medical thermography.* The heat image recorded by thermography depends upon the temperature distribution of the skin. Pathological processes that are accompanied by a change in the local circulation in the skin or underlying tissues can be studied by thermography.

X-rays are generated in high-vacuum tubes which are energized at high voltage. Since the discovery of X-rays by Roentgen in 1895, radiology has played an important part both in diagnosis and therapy, using the property of ionising radiation. It would be hard to find anywhere in the annals of medicine so rapid an acceptance of such a revolutionary discovery. The use of barium meal for study of the gastrointestinal tract, followed by radio-opaque iodine contrast media enabled visualisation of gallbladder, kidney, pelvis and ureters and blood vessels. The main challenge in diagnostic radiology is to obtain maximum information with the smallest possible patient dose. Use of image intensification electronically has achieved this objective substantially. Digital substraction techniques and computer-assisted imaging have been the most spectacular recent advances in the field which have revolutionised the practice of medicine.

Radioactivity was discovered by Becquerel in 1896 but the medical use of radionuclides became possible only in the 1950's. Today Nuclear Medicine techniques provide a means of measuring quantitative, regional and total functions of many organs in a simple non-invasive manner.

The most fundamental principle of nuclear medicine is the *tracer principle,* invented by George Hevesy for which he received the Nobel Prize in 1944. The ability to administer chemical substances labelled with a radioactive tracer and then follow what happens to them within the body led to the concept of the dynamic state of body constituents. We now know that our body constituents are in the process of constant formation and breakdown, processes that can be abnormally speeded up or slowed down as the result of disease. The tracer principle and the dynamic state of body constituents occupy the central circle of nuclear medicine from which have extended ever widening large circles, the most recent being the use of the technique of positron emission tomography (PET) to study the relationship between brain chemistry and behaviour.

By means of positron emission tomography, we can now distinguish multiple infarct dementia from Alzheimer's disease and can pinpoint the site of origin of focal epileptic seizures. Dr. Henry Wagner and his group at Johns Hopkins have recently carried out the first successful imaging of neurotransmitter receptors in the living human brain. Up to now, the PET scanner has been used largely to provide a reflection of overall nerve cell activity. Now we can assess the activity of specific neurotransmitters, such as dopamine and serotonin. Mapping of neuroreceptors in the past has been limited to studies conducted during autopsy using autoradiography. Visualization and quantification of the many neuroreceptors in the human brain has now been shown to be possible.

For over a century, people have known that chemical activity within the brain accompanies mental activity. Only now is it possible to apply directly the sciences of chemistry and physics to the study of the human brain. We can now examine the relationship between brain chemistry and behaviour in normal persons and patients with neurological diseases, such as Parkinson's and Alzheimer's diseases, and psychiatric diseases, such as schizophrenia and manic-depressive illness. Today the new techniques of positron emission tomography has made it possible to observe and measure the chemical reactions that occur within the brain and to relate these chemical changes to mental and behavioural activity.

It is not too much to hope that the new knowledge of brain function and chemistry may help us solve some of the problems of mental disorders that appear to be endemic to the human species.

The first medical studies of human beings with radioactive tracers began in the 1920's when Blumgart and his associates in Boston studied the velocity of the circulation in health and disease. The first studies of the thyroid were begun in the early 1940's by Hertz in Boston and Hamilton in Berkeley, California. It has taken four more decades to extend these biochemical studies of the thyroid to studies of the chemistry of the brain in living human beings. During that period nuclear medicine procedures have become widely used in medical diagnosis.

Ultrasound is a form of energy which consists of mechanical vibrations the frequencies of which are so high that they are above the range of human hearing. Most biomedical applications of ultrasound employ

frequencies in the range of 1 – 15 MHZ (mega hertz). The most commonly used transducer material is the synthetic ceramic lead zirconate titanate. This material is polarized during manufacture to make it strongly piezo-electric, that means it will create an electric current on being deformed by sound waves. As a safe and versatile non-invasive technique, ultrasound is being increasingly used in all areas of medical investigation (See Table I).

TABLE I

Ultrasound in Medicine

★ Imaging moving targets (eg. heart, fetus), soft tissues, blood flow.

★ Guided biopsy and aspiration.

★ Follow-up of treatment; radiation therapy planning.

Skull

(infant with open fontanelles) Hydrocephalus, hematoma

Eye and Orbit

Intra-ocular lesions in eyes with opaque media
Intra-ocular tumours, foreign bodies
Retinal detachment, vitreous haemorrhage
Exophthalmos – unilateral and bilateral

Thyroid

Nodules – solid Vs cystic

Heart

Ventricles: size, volume, wall thickness, wall motion ejection fraction, rate of circumferential shortening
Atria: dilatation, thrombus, tumour (myxoma)
Interatrial and interventricular septum defects
Valve structure,function, cross-section of orifices, vegetations, calcification
Pericardial effusion, thickening, adhesions, calcification
Pulsed doppler: Quantitation of regurgitant flow, velocity of blood flow in arteries and veins, patency of vascular grafts

Kidneys

Renal failure: differentiation of obstructive Vs parenchymal lesions
Renal mass: Solid Vs cystic
Guided dissolution of stones

Pancreas

Acute pancreatitis: differentiation from other causes of acute pain
Pancreatic pseudo-cyst
Pancreatic cancer

Liver and Gall Bladder

Mass lesions: differentiation of solid Vs cystic
Jaundice: differentiation of intrahepatic Vs extra hepatic causes
Gall bladder: Size, location, configuration, gall stones, choledochal cyst
Diaphragmatic movements, ascites

Obstetrics

Measurement of foetal age and growth
Foetal distress, foetal death
Foetal abnormalities: anencephaly, hydrocephalus, spinabifida, meningomyelocele etc.
Diagnosis of twin or multiple pregnancy, Hydatidiform mole, hydramnios, fibroids and cysts with pregnancy
Location of placenta: placenta praevia
Amniocentesis: fetal sex determination, genetic and metabolic defects

Gynaecology

Pelvic masses: fibroids, cysts, neoplasms
Localization of intra-uterine contraceptive devices
Suspected ectopic pregnancy; missed abortion
Pelvic abscess – diagnosis and follow up
Primary amenorrhoea; absent or hypoplastic uterus, polycystic ovaries

Concept of Mass, Weight and Density

Matter can be defined as that which has mass and occupies space. When an object is placed on a scale it registers a certain weight, which means that the force of gravity pulls this object towards the earth to a degree measured by the lowering of the scale's platform. The greater the attraction between the earth and the object, the greater the weight of the object.

A man in space encounters a situation where neither he nor the objects around him seem to have any weight. Objects within a spacecraft not fastened down float about freely in their condition of "weightlessness". If interplanetary travel becomes a reality in the 21st Century, a 100-pound damsel would weigh only 20 pounds on the moon and about 37 pounds on Mars. But still the *mass* remains the same and occupies the same amount of space.

Density is a measure of the amount of matter in a given volume of space. Thus the greater the amount of mass in a certain space, the greater the density. Density is itself independent of size.

With the widespread application of X-ray Computed Tomography or CT more attention is being paid to tissue density differences (bone having the maximum electron density, air the least) as an aid in diagnosis. Water is given the density number of 0, fat – 1000 and bone + 1000 on an arbitrary scale called Hounsefield numbers (in honour of the inventor of the technique of computed tomography).

Nuclear Magnetic Resonance (NMR)

Most of the body is water (70%) and the hydrogen component of water (H_2O) has unique properties which form the basis of nuclear magnetic reasonance imaging.

Elements whose nuclei contain odd number of protons or neutrons have an internal angular momentum or spin. The nucleus of hydrogen consists of a single proton, with a single orbital electron. Like a spinning top which also wobbles around its vertical axis, the hydrogen protons also spin and have a wobble called precession. They behave like very tiny bar magnets of a definite strength or magnetic moment. If they are placed in a magnetic field, they will line up more or less parallel to that field and will precess around it. If now they are exposed to radiofrequency (RF) stimulus, they will absorb energy and change their alignment in 90° or 180°. After the RF is removed the absorbed energy is released, the strength being proportional to the proton density. The nuclei eventually return to their original orientation. This process is known as relaxation. The variables T1 and T2 are called the spin-lattice relaxation, and spin-spin relaxation respectively. With the help of computer and applied mathematical techniques an image of proton density and T1, T2 relaxation, is produced by mathematical reconstruction, in cross-sectional as well as other orientations as desired (sagittal, coronal etc.).

The great promise of NMR is the ability to show differences in T1 elaxation times between normal and abnormal tissues. Malignant issues (and even pre-malignant tissues) generally have longer relaxaion times which differ significantly from normal. The findings that hemical and physiological alterations as revealed by NMR *precede* hanges in histology or anatomy makes NMR potentially a very senitive diagnostic method to detect disease at a very early stage. One can

now think in terms of detection of chemical alterations in disease at the cellular level in the living human beings.

NMR Spectroscopy

The technique of NMR Spectroscopy (NMRS) arose out of a basic discovery more than 30 years ago in nuclear physics, the magnetic properties of certain nuclei. In the NMR spectrometer the spinning atomic nucleus is placed in a strong magnetic field which causes them to line up in the field like a tiny bar magnet. The hydrogen or proton NMR spectrum of an organic molecule provides much information about its chemical structure, a feature that makes NMR invaluable to organic chemists. For example the NMR spectrum of a simple molecule ethanol (CH_3 CH_2 OH) consists of three separate resonance peaks representing the hydrogen nuclei in the three chemical groups CH_3, CH_2, and OH. Biochemists are more interested in reactions involving carbon and phosphorus ions and hence utilise C-13 and P-31 as markers instead of hydrogen.

The Bell Laboratory workers monitored the glycolysis of Escherichia coli with the aid of glucose incorporating C-13 at C_1 position in the molecule. The rest of the carbon atoms in the molecule were the common C-12 which do not exhibit magnetic resonance. The path of C-13 labelled carbon through the metabolic machinery of the cell could be followed (against the invisible background of thousands of simultaneous reactions involving C-12) by recording the spectrum of E. coli cells at one minute intervals.

In another series of experiments NMR peaks obtained from isolated rat liver cells were compared with profiles of known compounds. While observing the conversion of glycerol to glucose they detected the presence of lactate. When ammonia was added to the cells, C-13 showed up in alanine and aspartate and glutamate, revealing the activation of additional pathways based on metabolism of glucose. In this way complex interrelationships among the various metabolic pathways can be explored quantitatively with NMR spectroscopy (NMRS).

One of the most exciting biochemical applications of NMRS has been to measure pH inside the living cells. The Bell Laboratory workers suspended liver cells in phosphate-free buffer and added unlabelled glucose and phosphate enriched with P-31. In the NMRS of the respiring cells the resonance peak had two components suggesting the existence of a pH gradient.

To prove that the gradient existed between the mitochondria and the surrounding cytoplasm, the investigators added valinomycin which increases the rate of cell respiration and establishes an equilibrium in the concentration of H ions on both sides of the mitochondrial membrane. The drug would therefore be expected to speed up the efflux of protons from the mitochondria and increase the pH difference between the mitochondrion and surrounding cytoplasm. The valinomycin indeed caused the phosphate resonance to split into two distinct peaks. Conversely the drug FCCP which inhibits the active transport of protons across the mitochondrial membrane, caused the two phosphate peaks to collapse into one. These findings provide impressive support for the chemiosmotic hypothesis (that biological oxidation generates a proton gradient across the membrane of the mitochondrion, which in turn provides the free energy for the formation of ATP).

A wide range of biological preparations are suitable for investigations with NMRS, including bacterial cells, animal cells, isolated cell organelles and even entire isolated organs such as the heart and liver.

Biomedical Engineering

A remarkable development in 20th century Medicine is the interface of medicine and engineering which has been immensely productive in terms of benefits to the patients. For the medical men, it is very fascinating how engineers view medical problems. For instance when the engineer looks at the heart and circulatory system, from the hydrodynamic viewpoint he considers two pumps and two impedances connected in series to form a closed circulatory system. An analogy can be drawn between the hydraulic quantities of the circulatory system and the electrical quantities of a circuit. The electromotive force corresponds to the blood pressure, ER and EL, the current to the flow, I, and the electrical impedance to the hydraulic impedance Zp and Zs. The impedance has a real component which is dependent on the blood's viscosity and the length and radius of the blood vessels. It also has an imaginary component, which is dependent, both on the elasticity of the vessel wall (capacitive component) and on the mass of the blood etc. (inductive component). A hydraulic analog to Ohm's Law can then be used to relate the above quantities: $ER + EL = I\ (Zp + Zs)$.

Engineers have prepared block diagrams for various control systems in the human body, such as respiratory control, control of circulation and blood pressure, temperature regulation. The analog computer has

been extensively used in mathematical models of human control systems.

Medical Instrumentation

The role of Biomedical Technology in the practice of modern medicine can be gleaned by a look at Table II. Only one or two areas will be selected for discussion. To permit inspection of body cavities not visible to the naked eye, a tubular optical instrument known as *endoscope* is used. The quality of the image seen is dependent not only on the properties of the optical lens system but also on the illuminating system. In modern flexible endoscopes fibre optics are used to transmit light from an external light source. Fibre optics have good transmitting properties, so the system yields a high enough intensity of illumination to take colour pictures. The introduction of fibre optics has enabled the design of flexible endoscopes over their whole length. Thus one can now visualise the esophagus, stomach and duodenum, and the whole of the colon.

A wide variety of measurements are made in medical diagnosis.

The common theme of all measurements in clinical medicine is:

(1) detection of the signal by an appropriate transducer—eg. pH, pressure, flow.

(2) amplification of the signal and conversion to an electrical signal, usually a voltage pulse.

(3) Quantitation, record and display of results. With the advent of microprocessor technology many of the measurements are automated and displayed "on line".

Radiotherapy

Radiation therapy is based on two fundamental disciplines, radiation biology and radiation physics. Radiobiology is that branch of science that deals with the effects of ionising radiation on cells and tissues. Radiation physics is the branch of science that deals with ionising radiation.

In radiotherapy different types of radiation are used. A distinction is drawn between conventional X-ray therapy in which the radiation photon energy is less than 0.5 MeV and supervoltage therapy (mega volt or million volt). The high energy greater than 0.5 MeV can be obtained from radionuclides such as *Cobalt – 60*, or it can be generated by betatrons, linear accelerators and Van de Graaf generators.

The Computer Revolution and Medicine

Over the last 15 years the medical sciences have provided both physicians and patients with dramatic and new diagnostic and therapeutic tools and amenities. Many of these new technologies are coupled to computers and electronics. Computerised X-ray Tomography, intensive care monitoring, and automated laboratory instruments are already familiar to most of us. A most remarkable thing is that while computers are getting smaller, faster and more reliable, their cost is decreasing, hence their more widespread use.

The human mind is unsurpassed in the ability to perceive, think, analyse, imagine and to create, but is greatly limited in the ability to *store* large numbers of facts permanently, and to *recall* the data precisely and instantly. The computer can store, process and recall information far more effectively than the human brain. Clinical medicine is increasingly seeking quantitative measurements and concrete observables in the elaborate definition of disease. Medical knowledge and medical literature have grown to unmanageable proportions. Present computer technology argues strongly for an integrated computer system to provide information in a *timely* fashion, thereby improving the effectiveness of clinical practice and introducing audit procedures for quality assurance in medical care. Medical Information Science (MIS) has emerged as a distinct discipline that concentrates on the problems that arise when one attempts to integrate the rich knowledge base and behavioral variety of health care with the logical constraints of computer oriented information processing.

The profound and pervasive impact of the Computer is already felt in hospitals in most advanced countries. In many medical centres in U.S.A. some patients sit down at a computer terminal before meeting the doctor, to provide their medical histories and receive information about the hospital. In has been found that the patients tend to give a more candid account of their symptoms, regimen and past history to a computer programmed to ask the proper questions, than to a harassed and possibly intimidating doctor. Evidently the elements of fear, concealment and subsconcious repression are less operative when dealing with a machine.

In many hospitals medical data generated on the patient are stored and constantly updated as results of new tests are added on to the data base. The efficiency and scope of clinical laboratory procedures and advanced analytical instruments are greatly increased by computerisation.

Careful applications of computers have improved interpretation of diagnostic tests such as EEG and ECG. Many computer programmes are now helping the physicians to maximise the likelihood of correct clinical decisions. Computers are potential expanders of the physicians' information and knowledge resources.

The handicaps suffered by patients through loss of limb, paralysis, speech impediment, deafness and blindness affect their quality of life and job opportunities. Microelectronics and computers come to the aid of the patient in overcoming these functional deficiencies. Computers have been incorporated in prosthetic devices. Microprocessors have made possible the development of light-weight, manoeuvrable and reliable electrically powered wheel-chairs. Microelectronic-operated portable reading aids for the blind are now available.

TABLE II

Biomedical Engineering Technology

I. Clinical Diagnosis

Electrocardiography and Vectorcardiography.
Holter monitoring, biotelemetry, ambulatory monitoring.
Electroencephalography—Evoked potentials
Electro-oculography, electroretinography
Electromyography & nerve conduction studies
Audiometry, brain stem evoked response
Phonocardiography
Plethysmography
Ultrasonography and pulsed Doppler
Thermography
Fiber-optic endoscopy, ophthalmoscopy, arthroscopy
Radiology
Cardiac catheterization and coronary arteriography
Digital subtraction Angiography
X-ray computerised Tomography
Emission Computerised Tomography
Radionuclide Techniques
NMR imaging and spectroscopy

II. Clinical Chemistry and Laboratory Diagnosis

Automated Clinical Chemistry & Haematology
Light microscopy, electron microscopy, fluorescent microscopy

Radioimmunoassay (RIA)
Enzyme-linked Immunosorbent assay (ELISA)
Electrophoresis & Immunoelectrophoresis
Chromatography, liquid, gas, HPLC
Neutron Activation Analysis
Spectrophotometry, flame photometry, fluorometry
Ultracentrifugation
Microbiology—radiorespirometry
Serology, Immunology
Hybridoma technique—monoclonal antibodies

III. Therapeutic
Electro-convulsive therapy
Cardiac pace makers
Cardiac defibrillators
Aortic balloon pumps
Pump-Oxygenators (Heart Lung Machine)
Ventilators—Volume cycled & pressure cycled
Hyperbaric oxygen
Haemodialysis and peritoneal dialysis
Haemoperfusion
Plasmapheresis
Hypothermia and hyperthermia
Biofeedback techniques

IV. Surgical
Anaesthesia equipment
Surgical diathermy and electro-surgery
Cryosurgery techniques
Lasers – Argon, Xenon, Yag
Steriotactic techniques
Microvascular surgery

V. Intensive Care Monitoring
Foetal monitoring, neo-natal intensive care monitoring
Central venous pressure, blood gases
Swan-Ganz Catheter – LA pressure
Intra-cranial pressure monitoring

VI. Prostheses
Artificial heart
Artificial Heart Valves

Implantable prostheses
Vascular grafts – dacron, teflon
Joints – Hip, Knee etc.
Artificial ear, artificial mastoid, artificial larynx
Artificial limb
Myo-electrically controlled prostheses
Computerized aid for the physically handicapped

VII. Genetic Engineering

Production of human insulin
Production of human growth hormone
Production of human interferon

VIII. Radiotherapy

Cobalt
Linear Accelerator
Cyclotrons & Van de Graaf Generators
Fast neutrons, heavy ions and mesons
Neutron Capture therapy

IX. Physical Therapy

Infra-red
Short wave diathermy, ultra-shortwave 690 mm
Microwave therapy 120 nm
Ultrasonic therapy 1 MHZ
Phototherapy with UVR-A, UVR-B

X. Sterilization

Autoclaving – steam, dry heat
Chemical sterilization – gas, liquid
Radiation sterilization of instruments
Ultraviolet lamps
Air Filters, lamellar flow
Millipore filters for instant sterilization of I.V. material

XI. Medical Information System (MIS)

Computerized Medical Records
Computer – analysis of data – ECG, Holter, EEG, Chromosomes etc.
Computer-assisted diagnosis
Computer-assisted medical instruction
Computer-assisted pharmacy & prescribing
Intensive Care – automation in therapy
Literature Search

Chapter 7

THE CHEMISTRY OF LIFE

Introduction

In *Charaka Samhita* (Chikitsa Sthanam, Chapter 15, Stanzas 22 – 27) we come across the following queries:

"How is blood produced in the body from nutrient fluid which has no resemblance to blood?"

"The nutrient fluid has no redness. How then does it obtain the redness of the blood?"

"How again is the solid flesh in men produced from the fluid blood?"

"How is the fluctuating element, fat, produced from firm flesh?"

"Again, how is the roughness of bones produced from the smooth flesh and fat?"

"How is the soft and unctuous marrow produced inside the bones which are hard?"

"If the semen is born out of the change in the marrow, and if as the wise say, semen is in the entire body and the marrow which is inside the bones becomes semen, how does it flow out, as there are no holes or leaks in the bone?"

The questions are very interesting and show the spirit of scientific curiosity. Charaka and Sushruta tried to answer these questions in the light of the then prevalent concepts. In the light of today's knowledge we are naturally inclined to look at the old ideas with disdain, but it is well to remember that they were intended to explain the biological phenomena observed in terms of the knowledge existing at that time.

20th Century Revolution in Biology

In the 20th Century, a revolution took place in the life sciences with a profound impact on our thinking. For hundreds of years the inanimate

world was far better understood than the world of living things. Physicists began their studies by examining such fundamental qualities of matter as mass, force and motion, which have been applied in every field from the astronomic to the microscopic. Biologists, on the other hand had no comparable universals on which to base their science, hence the ancient Indians in their intuitive wisdom postulated the concept of *Vata, Pitta* and *Kapha* as a biological doctrine to explain phenomena in the living, human, ánimal as well as plants. For among living things no single set of characteristics seemed more fundamental than another, consequently it seemd beyond hope, until recently, that biology could yield the kind of broad comprehensive understanding that physics has achieved.

In the last 30 years, the life sciences have formed revolutionary ways to connect the general to the specific. Scientists discovered that when nutrient fuels are broken down within living organisms, the energy released is stored in the high energy bonds of a compound called ATP (adenosine triphosphate). ATP is found in the cells of *all* living organisms, from bacteria to man. The universal use of ATP as a common "energy currency" was an indication of the chemical unity of life.

The biggest break-through came in 1953 with the knowledge of the structure of DNA. The realisation that virtually *all* life on earth uses the *same* complex molecules to store and transmit genetic information, resulted in a new understanding of living things. Their kinship became measurable with the same kind of precision that physicists had been able to employ in describing mass regardless of whether they were dealing with a feather or a chip of gold. Today biochemists can determine, for example, that the sequence of amino-acids in a certain protein molecule differs in a pig at 4 points from that of the same protein molecule in the rabbit, at 11 points from that in a frog, at 27 points from that in a moth, and at 47 points from that in a cauliflower.

Twentieth Century biology provides reasonable answers to the queries raised in the introductory part of this chapter. To understand these answers, it would be first necessary to become familiar with the main advances in biology and bio-chemistry, with particular reference to the unit of life, the cell, the proteins and enzymes, and metabolic pathways and the energy transformation in the cells.

Cell, the Unit of Life

The fact that all organisms are made up of cells was not recognized until the 19th Century. In 1676, Antony van Leeuwenhoek (1632 – 1723)

reported his observations of "an incredible number of little animals of diverse kinds" through his microscope.

The invention of the microscope enabled the study of living tissue under magnification which the unaided eye could not achieve. Based on such studies the botanist Matthias Schleiden and the zoologist Theodor Schwann proposed in 1839 that tiny cells are the basic units of life. Any organism visible to the naked eye is actually a population or colony of billions of individual cells. Schwann believed that they developed by spontaneous generation from an undifferentiated homogeneous substance termed "blastema". By detailed experimental study Rudolf Virchow (1821 – 1902) disproved blastema theory and was able to assert unequivocally, in 1859, that "we can now go so far as to establish as a general principle, that no development of any kind begins de novo. When a cell arises, there a cell must have previously existed *(omnis cellula e cellula).* Every organism arises from the union of two single germ cells, the egg and the sperm. The cell formed by this union then divides into two daughter cells, each of which in turn grows and divides to produce its own daughter cells.

Since cells are concrete objects and can easily be observed, the experimental investigation of cells thereafter displaced philosophical speculations about the problems of life and the uncertain scientific studies that had pursued such vague concepts as "protoplasm".

By the end of the 19th Century, improvements in microscope design and in the techniques of preparing living tissues for microscopic observations had brought into view the interior structure of cells and the mechanism of cell division. In particular, it was found that cells contain a *nucleus* and that within this nucleus is present a well-defined set of thread-like bodies, the *Chromosomes.* Before cell division, each chromosome splits into two and during cell division the chromosomes are distributed in such a way that each daughter cell is given its own complete chromosome set. The observation of this regularity in the distribution of chromosomes led to the idea that chromosomes are carriers of heredity. Thomas H. Morgan and his associates showed that the carriers of hereditary information, the *genes,* are arranged in a linear order on the chromosomes. Furthermore, genes were found to be capable of undergoing *mutations,* or sudden permanent changes, such as change from red flower colour to white.

Rise of Modern Biochemistry

The 20th Century will be remembered for its scientific advances. It has seen great developments in the field of physics: Einstein's Theory of

Relativity, the elucidation of the structure of the atom, nuclear fission and nuclear fusion, and explosion in the field of particle physics. The tools that grew out of these major advances—ultraviolet spectroscopy, infra-red spectroscopy, electron spin resonance, nuclear magnetic resonance, X-ray crystallography, and mass spectrometry—have provided the means by which chemists could embark on the analysis and synthesis of complex structures and an understanding of chemical reactions on a more rational level. What is more interesting, and relevant, its impact on biology has permeated to medical thinking and medical concepts of today.

The synthesis of urea by Friedrich Wohler in 1828 was the first demonstration that a "natural" and "organic" product of biological origin differed in no essential way from non-biological matter and could be artificially synthesized from its elements; urea was obtained by boiling an aqueous solution of ammonium cyanate (NH_4CNO_3).

The word bio-chemistry was first used by Hoppe-Seyler in 1877. In the last hundred years biochemistry has made great strides and today biochemistry dominates medical thinking. Modern biochemistry is primarily dynamic biochemistry. This comprises the various aspects of metabolism, synthesis, degradation and conversion—and a study of the enzymes that catalyze these reactions. Since these unceasing changes take place in an orderly fashion, regulation has been another area of investigation. Dynamic biochemistry is also concerned with all those chemical processes that take place on the structural elements within the cell, and a new field of supra-molecular biochemistry is slowly emerging. Apart from organic chemistry, the rapid growth of physical chemistry at the turn of 19th Century was an equally important factor in the development of modern biochemistry. Kinetics, bioenergetics, thermodynamics, electrochemistry, electrolyte behaviour and so forth, and the availability of new and highly sensitive physico-chemical methods were just as necessary and indispensable.

Proteins

"There is present in plants and in animals a substance which is without doubt the most important of all the known substances in living matter, and without it, life would be impossible on our planet. This material has been named Protein".

So wrote Gerard Johannes Mulder, a Dutch agricultural chemist in 1836. It was in his scientific papers that the word *protein,* from the Greek proteios, meaning "of the first rank", made its first public appearance. The word had been suggested to him by the great Swedish

chemist Jons Berzelius (who also introduced to chemistry "Catalysis", "Polymer" and other important terms). Mulder and his great German contemporary Justus von Liebig thought that protein was a single substance, a basic structural unit existing in the same form in materials as diverse as egg white and blood fibrin; this was soon found to be an error. The number and variety of proteins was found to be legion.

The proteins are one of the three principal organic constituents of living matter (the fats and carbohydrates are the others). They represent nearly one half of the body's dry matter (about 70 per cent of the body is water). Of the total body proteins, more than a third is found in muscles. The protein *myosin* forms the fibres that are the fundamental contractile elements in muscular movements. The bones and cartilage account for another 20 per cent, here the protein *collagen* contributes to the structural stability of the skeleton. And the skin has about 10% of the body protein, the skin protein *keratin* serving to protect the interior tissues against attack from the external environment. Another protein, *haemoglobin* serves the function of oxygen transport.

Perhaps the most important of the proteins are the *enzymes*. These substances are present in only minute amounts in comparison to myosin, collagen or keratin, but they are indispensable for the promotion and direction of the body's myriad chemical reactions; thus the digestion of food stuffs in the stomach and the intestines depends upon the continuous activity of protein enzymes such as pepsin and trypsin. It is the synchronised action of a series of enzymic proteins that enable the body cells to use oxygen, to oxidize the carbon and hydrogen in food and thereby provide the major portion of the chemical energy. This energy is used not only for muscular movements but also to counteract the wear and tear of living tissues by the continuous regeneration of body constitutents, including the proteins, under the specific directive influence of a host of other enzymes.

Many *hormones* are also proteins; these remarkable products of the secretory activity of the endocrine organs are carried by the blood stream in infinitesimal amounts to the tissues, where they play a decisive role in the regulation of the pace and directions of metabolism. Still other proteins are the *antibodies* of the blood which defend the organism against viruses (which are themselves a nucleic acid core with protein envelop), and the bacterial toxins.

Where there is such a diversity of functions there must be a corresponding diversity of chemical structure. The number of identified

proteins is extremely large. To study the chemical structure of a particular protein it is necessary to extract the protein with a suitable solvent, such as a dilute salt solution. This procedure inevitably brings into solution many of the other proteins present in the cell, and the task of separating the desired proteins from the unwanted materials demands great skill.

Shortly after 1880, the technique of "salting out" was developed whereby a protein is precipitated by adding a salt at high concentration. Different proteins required different concentrations of salt to precipitate them, so that separation of different protein fractions was possible. Wilhelm Kuhne achieved purification of proteins by high concentration of sodium or ammonium sulphate. The addition of organic liquids such as ethanol or acetone to aqueous protein solutions was another powerful method of protein precipitation. Hofmeister described the first preparation of crystalline protein, serum albumin.

By careful control of factors such as salt concentration, alcohol concentration, acidity and temperature, fairly selective precipitation of a given protein may be achieved. Many individual proteins have been obtained in the form of crystals which may be recrystallized at will, thus leading to further purification. The availability of crystalline proteins has for the first time given to the biochemist reproducible material for the study of the chemical nature of these substances. All proteins are made principally of carbon, hydrogen, oxygen and nitrogen. It is the nitrogen representing from 12 to 19 per cent of the molecule that is the special mark of a protein. Most proteins also contain a small amount of sulphur and many have some phosphorus.

The Swedish physical chemist Svedburg in 1926 devised an ultra high speed centrifuge in which the proteins are spun at speeds upto 70,000 revolutions per minute, which develops a centrifugal force as much as 400,000 times that of gravity. In such a field large protein molecules move outwards from the centre of rotation with selective speeds; the larger they are the faster their motion. An ingenious optical apparatus measures the rates of this molecular sedimentation and the molecular weight can then be calculated. These measurements show that the smallest known protein insulin has a molecular weight of 4500, that means it is 4500 times as heavy as hydrogen. The largest known proteins have molecular weights of the order of 10 million. The protein molecule can be cleaved into smaller molecules of its constitutent amino-acids. This is achieved by treatment with acids or alkalis; because water enters into the reaction, the process is called hydrolysis.

Amino-acids

One striking feature of 19th Century speculations about protein structure is their lack of emphasis on amino-acids as structural units of proteins. The simplest amino-acid glycine was isolated in 1820 by the French chemist Henri Braconnot; he obtained it by acid hydrolysis of gelatin. With the entry of Emil Fischer into the protein field, separation of amino-acids present in an acid hydrolysate of proteins was achieved. Fischer also introduced the term "peptide" and isolated well defined dipeptides (e.g. glycine-alanine) from a partial acid hydrolysate of a protein. By 1906 about 15 amino-acids were recognised to be protein constituents. The list of known amino-acids from proteins has now grown to 22. Every amino-acid except glycine can exist in two geometrical forms, one the mirror image of the other. By convention these are designated the "L" (levo) and "D" (dextro) forms. Only the "L" type of the amino-acids is obtained by the hydrolysis of proteins.

During the past 100 years an intensive effort has been devoted to the development of experimental methods for the accurate quantitative determination of the relative amounts of various amino-acids formed by the hydrolysis of a protein. An ingenious technique called chromatography invented by the Russian botanist Michael Tswett in 1906, was applied by the English chemists A. J. P. Martin and R. L. M. Synge to the separation of amino-acids. They introduced the use of a starch column as the absorbent, for the quantitative separation and analysis of amino-acid constituents of proteins. These methods made it possible for Sanger to attack the problem of the amino-acid sequences of insulin. The longest peptide sequence that has been established is B-galactosidase with 1100 amino-acid residues. Collagen and pro-collagen have around 1200 amino-acid residues.

Haemoglobin Structure and Respiratory Transport

John Desmond Bernal taught at Cambridge in England in the 1930's that the riddle of life was hidden in the structure of proteins and that X-ray crystallography was the key to solving it. Perutz and his colleagues unravelled the architecture of the haemoglobin molecule in 1959.

Haemoglobin is the vital protein that conveys oxygen from the lungs to the tissues and facilitates the return of carbon dioxide from the tissues back to the lungs. These functions and their subtle interplay also make haemoglobin one of the most interesting proteins to study. A haemoglobin molecule is made up of four polypeptide chains, two

alpha chains of 141 amino-acid residues each, and two beta chains of 146 residues each. The alpha and beta chains have different sequences of amino-acids, but fold up to form similar three-dimensional structures. Each chain harbours one *haem,* which gives blood its red colour. The haem consists of ring of carbon, nitrogen and hydrogen atoms called *porphyrin,* with an atom of iron, like a jewel at its centre. A single polypeptide chain combined with a single haem is called a sub-unit of haemoglobin or a *monomer* of the molecule. In the complete molecule four sub-units are closely joined, as in a three-dimensional jig-saw puzzle, to form a *tetramer.*

Haemoglobin function

In red muscle there is another protein, *myoglobin* similar in constitution and structure to a beta sub-unit of haemoglobin, but made up of only one polypeptide chain and one haem. Myoglobin combines with oxygen released by red cells, stores it and transports it to the subcellular organelles called mitochondria, where the oxygen generates chemical energy by the combustion of glucose to carbon dioxide and water. Myoglobin was the first protein whose three-dimensional structure was determined in 1957 by John Kendrews and his colleagues at Cambridge, in England.

Myoglobin exists for the sole purpose of allowing its single atom of iron to form a loose chemical bond with a molecule of oxygen (O_2). Why does nature go to so much trouble to accomplish what is apparently such a simple task? Like most compounds of iron, haem by itself combines with oxygen so firmly that the bond, once formed, is hard to break. Normally ferrous (carrying 2 positive charges) haem reacts with oxygen irreversibly to ferric haem (carrying 3 positive charges). But when ferrous haem is embedded in the folds of the globin chain, it is protected so that its reaction with oxygen is *reversible.* Moreover in the protein the iron is linked to a nitrogen atom of the amino-acid histidine, which donates negative charge that enables the iron to form a loose bond with oxygen.

An oxygen-free solution of myoglobin or haemoglobin is purple in colour, like venous blood. When oxygen is bubbled through such a solution, it turns scarlet like arterial blood. If these proteins are to act as oxygen-carriers, then haemoglobin must be capable of taking up oxygen in the lungs, where it is plentiful, and giving it up to the myoglobin in the capillaries of muscle, where it is less plentiful;

myoglobin in turn, must pass the oxygen on to the mitochondria where it is still scarcer.

Carbon monoxide (CO) combines with the haem iron at the same site as oxygen, but its affinity for that site is 150 times greater; carbon monoxide therefore displaces oxygen, which explains why it is so toxic. In heavy smokers upto 20 per cent of the oxygen-combining sites can be blocked by carbon monoxide so that less oxygen is carried by the blood.

The carbon dioxide released by tissue respiration is too insoluble to be transported as such, but it can be rendered more soluble by combining with water to form a bicarbonate ion and a proton. The chemical reaction is written thus:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

In the absence of haemoglobin this reaction would be soon brought to halt by the excess of protons produced, like a fire going out when the chimney is blocked. Deoxyhaemoglobin acts as a buffer, mopping up the protons and tipping the balance towards the formation of soluble bicarbonate. In the lungs the process is reversed. There, as oxygen binds to haemoglobin, protons are cast off driving CO_2 out of solution so that it can be exhaled. The reaction between CO_2 and water is catalysed by an enzyme in the red cell, *Carbonic anhydrase,* which speeds up the reaction to a rate of about half a million molecules per second, one of the fastest of all known biological reactions.

Haemoglobin is the prototype of protein molecules that change their structure in response to chemical stimuli—deoxyhaemoglobin has a different structure from oxyhaemoglobin. The hemoglobin molecule is assumed to have two alternative structures, designated T for tense and R for relaxed. Taking an analogy of spring clamps, in the T structure the subunits of the molecule are clamped against the pressure of springs and their narrow pockets impede the entry of oxygen. In the R structure all the clamps have sprung open and the haem pockets are wide enough to admit oxygen easily. The transition between the two structures is influenced by several factors including protons, carbon dioxide, chloride and DPG (diphosphoglycerate). Increasing the concentration of any of these factors shifts the oxygen equilibrium curve to the right, towards lower oxygen affinity and makes it more sigmoid. The more pronounced the sigmoid shape of the equilibrium curve is, the greater the fraction of oxygen that can be released. With a typical sigmoid curve nearly half of the oxygen carried can be released to the tissue.

The human fetus has a haemoglobin with the same alpha chains as in the adult haemoglobin but different chains than beta, resulting in a lower affinity for DPG. This gives fetal haemoglobin a higher oxygen affinity and facilitates the transfer of oxygen from the maternal circulation to the fetal circulation. How subtle changes in amino-acids lead to changes in the function of haemoglobin is shown in Table II in the chapter on Genetics (page 177).

Protein Synthesis

A cell builds protein from amino-acids it takes from its surroundings. All proteins are built up by linking amino-acids end to end. Each of the 20 different amino-acids has a carboxyl group ($-COOH$) at one end and an amino group ($-NH_2$) at the other. To link the Carboxyl group of one amino-acid to the amino group of another amino-acid a molecule of water must be removed, producing an amide linkage ($-CO\ NH$). The carbon adjacent to the amide linkage is called the alpha carbon. It is important because each amino-acid has a distinctive side-chain at this position. The side-chain may be nothing more than a single atom of hydrogen (e.g. glycine) or it may consist of a number of atoms, including a six-carbon aromatic ring (i.e. phenylalanine, tryptophane and tyrosine).

The 20 amino-acids can be grouped into 3 broad classes depending upon the character of their side chains. Five are *hydrophilic* or water-loving, and tend to acquire either a positive or negative charge when placed in aqueous solution. Three of them are basic (arginine, histidine, lysine) and two are acidic (aspartic acid and glutamic acid).

Hydrophobic amino-acids, not readily soluble in water are 7 in number, including the three with aromatic ring, plus leucine, isoleucine, methionine and valine.

Ambivalent amino-acids (in their reaction to water) are 8 in number, alanine, asparagine, cystine, glutamine, glycine, proline, serine and threonine.

The energy for protein synthesis is provided by the oxidation of phosphoglyceroaldehyde, an important intermediate compound in the metabolism of carbohydrates when it is oxidized; this compound is coupled by a likely enzymatic reaction with inorganic phosphate to form phosphoglycerylphosphate; the latter then delivers its phosphate to adenosine diphosphate to form ATP, the famous biochemical energy carrier. In the third step ATP delivers a phosphate to an amino-acid,

thereby creating an amino-acid acylphosphate. Finally in a fourth step this amino-acid reacts with another, liberating inorganic phosphate and forming a dipeptide.

When an amino-acid chain is synthesized inside a cell, it is helped to fold in the proper way by the natural tendency of *hydrophobic* or "oily" side chains to retreat as far as possible from the aqueous environment and cluster in the centre of the molecule. The three-dimensional configuration of a protein molecule is determined uniquely by its amino-acid sequence, and short-range forces acting between the various parts of the molecule, for example Van der Waal forces, electrostatic attractions due to the electrical dipoles that all atoms induce in one another when they are close together.

A fascinating phenomenon is *self-assembly* whereby 2 alpha and 2 beta chains spontaneously aggregate to form the tetrameric haemoglobin molecule. Other examples are: the spontaneous aggregation of 12 molecules of pyruvate decarboxylase, 6 molecules of dihydrolipoyl dehydrogenase and 24 molecules of a transacetylase, each with its own coenzyme to form a supermolecule of molecular weight 5,000,000, superbly organized to accomplish the metabolism of pyruvic acid; the combination of three filamentous strands to form tropocollagen fibrils which then align side by side, and in register, to form tough fibres.

Enzymes

Until the end of the 19th Century it was generally thought that there is a secret chemistry of life whose reactions can be produced only in the living, intact cells, and therefore beyond the scope of study by the chemists' test tube methods. But in 1897 Edward Buchner showed that this is not so. Buchner made a paste from brewer's yeast, ground it with abrasive sand, and collected the juice released from the broken yeast cells. Buchner found that sugar is converted into alcohol and carbon dioxide gas bubbles; that is to say, the *cell-free* juice produced the same fermentation process in the test tube that the intact yeastcells carry out in the brewer's barrel. Study of the yeast cell juice then revealed that it contains agents that can promote specifically the chemical reactions of the fermentation process. These agents were given the names *enzymes,* a word derived from the Greek meaning "in yeast". Since enzymes capable of promoting a variety of other chemical reactions were soon found in extracts of many other cells, Buchner's discovery marks the beginning of *biochemistry.*

During the first 50 years of the 20th Century biochemists managed to work out most of the few thousand chemical reactions that go on in cells. These reactions mainly concern two general types of chemical processes. One is the *synthesis* of new cell components out of atoms and molecules taken up from the environment necessary to sustain life. The prime source of that energy is sunlight. Green plants absorb and convert sunlight into chemical energy by a reaction sequence called *photosynthesis.* In the 1950's the full details of photosynthesis, the most important reaction in biology, became known. Organisms other than green plants obtain energy from eating some of the green plants of their environment, or by eating some of the eaters of green plants.

The complex chemistry of the living cell is engineered by thousands of different enzymes, each of which is a catalyst for a particular chemical reaction.

The most important chemical reactions were found to be almost identical in all forms of life. No better proof of the truth of the Darwinian theory of common ancestry of all creatures could be desired than the lesson of the 20th Century biochemistry that all creatures make their living by use of more or less the same chemical processes. Almost every one of the chemical reactions of cell was found to depend on the presence of a particular enzyme that can promote that particular reaction. Hence the central problems for understanding of life processes became what enzymes are, how they work and how they are made. What enzymes are was discovered in 1926 by James Sumner; he found that enzymes are proteins. Studies of enzyme proteins during the last 40 years gradually showed that it is their particular specific structure that allows them to bind the atoms and molecules whose chemical reactions they promote. George Beadle and Edward Tatum proposed in 1940 that enzymes are made under instructions by the genes. Each gene determines a particular sequence of amino-acid constituents of the enzyme, and directs the synthesis of the enzyme, which in turn promotes a particular chemical reaction.

Four years after Beadle & Tatum's proposal that genes direct the synthesis of enzymes, in 1944 Oswald Avery and his associates discovered that genes are made of molecules of deoxyribonucleic acid (DNA). Avery was working with various types of pneumococci. He showed that in a bacterial culture, it was possible to transform a "rough" type colony into a "smooth" type by treating the former with DNA extracted from the latter. DNA had been first isolated from pus cell nuclei in 1868 by Friedrich Miescher. After the 1920's when

DNA was shown to be a major component of the chromosomes, the connection of DNA with genes was suspected, but one could not be sure of the true role of DNA until Avery showed that a cell lacking a particular gene can acquire that gene upon being presented with pure DNA molecules extracted from another cell (in this particular instance, a strain of pneumococci) known to possess that gene.

The most important single break-through that finally led to the understanding of the nature of the gene came in 1953, when James Watson and Francis Crick discovered that DNA is a double helix made up of two very long, structurally complementary, intertwined molecules. In 1961 Fancois Jacob and Jacques Monod proposed the 'operon theory of gene function'.

Next to each *structural gene* which specifies the amino-acid sequence of protein or enzyme, there lies on the chromosome another short length of DNA, the *operator gene* which regulates the rate of expression of the adjacent structural gene. The operator can exist in two states, open or closed, and the gene is expressed as long as the operator is open. The operator closes as soon as it combines with a specific protein molecule called the *repressor.* Thus it follows that the amount of a given protein or enzyme that a cell contains is governed by the repressor; the more repressor is available, for closing the operator of the gene that specifies the structure of the enzyme, the lower the rate of expression of that gene and hence the smaller amount of the enzyme that is produced.

Although each one of the billions of cells in the human body contains the same set of instructions of its chromosomes, different tissues have different kinds of cells performing very different functions. A human hair cell is obviously a very different thing from a human red blood cell or a human liver cell. How does a cell manage to differentiate itself from other cells that have descended from the same single fertilized egg? Since the character of any cell depends on the particular set of enzymes that it contains, it is obvious today that no real answer could have been given to that question before the role of DNA in directing protein synthesis had been understood. The process of *embryonic cell differentiation is now the focus of attention of molecular biology.*

In an astonishing stride forward in the history of biology, Ross. G. Harrison developed sixty years back, the technique of *tissue culture.* Early in the development of tissue culture as a research tool, Margaret and Warren Lewis demonstrated that fragments of embryonic chick skeletal muscle, embedded in clotted plasma, not only grow but form

striated muscle. Encouraged by the successful cloning of skeletal muscle, other workers have extended the approach to several other differentiated cell types of the chick embryo. Cardiac muscle, retinal pigment cells and cartilage cells have also been cloned showing that these differentiated phenotypes are stably inherited through many generations. Rat liver cells have also been cloned recently.

The heart of the chick embryo begins to beat on the second day of development. New chemical techniques now make it possible to investigate the formation of the heart at an even earlier stage. Heart myosin, a contractile protein, is synthesized very early by cells which are "programmed" to form the heart. The selective effects of various substances that interfere with normal cell chemistry have produced striking evidence that the heart-forming regions of the embryo are distinguished chemically well before structures of the heart appear. The locations of the cells destroyed by the metabolic inhibitor sodium fluoride, coincide with the sites that have the greatest capacity to form heart muscle, and with the areas that have the greatest capacity for the synthesis of actin and myosin.

Evidently in specific "morphogenetic fields", activation of specific genes is induced by chemical stimuli furnished by inducer substances.

When an organism containing several tissue types is experimentally dissociated into a mixture of individual cells, these cells can often reassemble into a pattern resembling that which they had in the original organ. During embryonic development, altered cell arrangements provide a continuously changing environment. Cells impinge upon and influence each other within that environment. The nature of those influences may be either cell-to-cell contact, or humoral or neuronal. There is increasing evidence that the developing nervous system plays an essential trophic role in the development of a large number of organs.

Today's developmental biologists raise the same questions that Charaka did: what leads a fertilized cell to divide, and to produce daughter cells which become as unlike as bone and muscle, blood and nerve? Many investigators are now studying the mechanisms underlying *differential gene expression,* the mechanisms whereby the activities of the genes are regulated.

Cell Lineage Studies

The identification of the genetic and molecular events that determine

how cells become different from one another during development, is the challenge to 20th Century biology. Sydney Brenner, director of the British Medical Research Council's Laboratory of Molecular Biology, Cambridge, England, chose a round worm *C. Elegans* as a tool to explore the grammar of development because of its very small size (one millimetre long) and small number of cells (roughly 1000) in its entire body. It has a short life cycle, the fertilized egg develops into the mature animal in only 3.5 days. The round worm is transparent which means that an observer can watch cells divided in the living organism. The complete cell lineage of *C. Elegans* has now been worked out, an achievement that will aid analysis of genes action in development. The cell lineage is a sketch map of development; with it we can trace the pathway of gene action at the level of single cells.

Basically what one gets out of the cell lineage studies is how different cells are related to one another. The cell lineage maps can identify the paths followed by cells as they become committed to one or another of their possible fates. With the help of the lineage map, mutations in the genes that affect cell fates can be identified. Studies of the genes can reveal when, where and how they control development.

Energy Transformation in the Cell

How does the living cell convert the energy of food-stuffs into a form that can be utilised and stored? The past three decades have seen great advances in the investigation of this riddle, which has engaged the minds and talents of some of the ablest investigators of the century. Our present understanding encompasses not only the chemical and physical aspects of the process but actually the molecules in the cell that conduct it. Many of the active molecules – the enzymes have been identified; the intricate chains and cycles of activity by which they extract, trap, exchange and distribute energy have been worked out in sufficient detail to illuminate their principles of operation (see Table I). The molecular machinery of these energy transforming functions has been securely located in the mitochondria.

The food intake supplies the fuel, sugars, fats and proteins, to the energy transforming system of the cell. Every student of elementary chemistry learns that a given weight of an organic compound contains a fixed amount of potential energy locked up in the bonds between the atoms of its molecule, for example the bonds between the carbon, hydrogen and oxygen atoms in the sugar glucose. The energy can be liberated by burning the sugar in oxygen, with the carbon and

hydrogen evolving from the flame in the relatively simple, energy-low molecules of carbon dioxide (CO_2) and water (H_2O). This oxidation yields 690,000 calories (690 K cal) per mole of glucose. (A mole is the weight of a substance in grams that is numerically equal to its molecular weight. A mole of glucose weighs 180 gms.) When the same amount of glucose is oxidised inside the cell, the same energy is available to the cell, with the same end products CO_2 and H_2O.

$$C_6H_{12}O_6 + 6O_2 + 6H_2O \rightarrow 6CO_2 + 12H_2O + 690 \text{KCal/mole}$$

Antoine Lavoisier, the father of modern chemistry demonstrated that respiration is a special form of oxidation and thus confirmed the relevance of chemical processes to the functioning of living organisms. What is the major difference between combustion of glucose in a flame and in a cell? The cell recovers the energy liberated by the oxidation of food stuffs not primarily as heat, but rather as chemical energy, a form of energy that can do work in a constant temperature system. To obtain energy in this useful form the cell oxidizes its fuel in a stepwise manner. The process by which glucose is broken down into carbon dioxide and water involves over thirty individual chemical reactions. Nearly everyone of these reactions is reversible. Still the overall process goes in one direction because the products from each individual reaction are used as reactants for the next reaction in the series. The catalytic agents of this controlled combustion are the enzymes, large molecules that function as catalysts or promoters of chemical reactions. The cell employs dozens of oxidative enzymes, each specialised to catalyze one reaction in the series that ultimately converts the fuel into carbon dioxide and water. As the energy is liberated in the stepwise breakdown and oxidation reactions, it is captured in the chemical bonds of the special energy storing molecule adenosine triphosphate or ATP. ATP may be regarded literally as fully charged storage battery. When the energy of this battery is withdrawn to make muscle contract, for example, the energy-rich ATP molecule transfers its energy to the contracting muscle by losing its terminal phosphate group. ATP (adenosine triphosphate) thus becomes ADP (Adenosine diphosphate), the storage battery in its discharged state. To "recharge" the battery, it is obviously necessary to supply a phosphate group plus the energy required to effect the uphill reaction that couples the phosphate to ADP. *Oxidative phosphorylation* provides the means for converting the energy released by oxidation into reconstruction of ATP. This conversion of the energy liberated by the combustion of fuel into the third

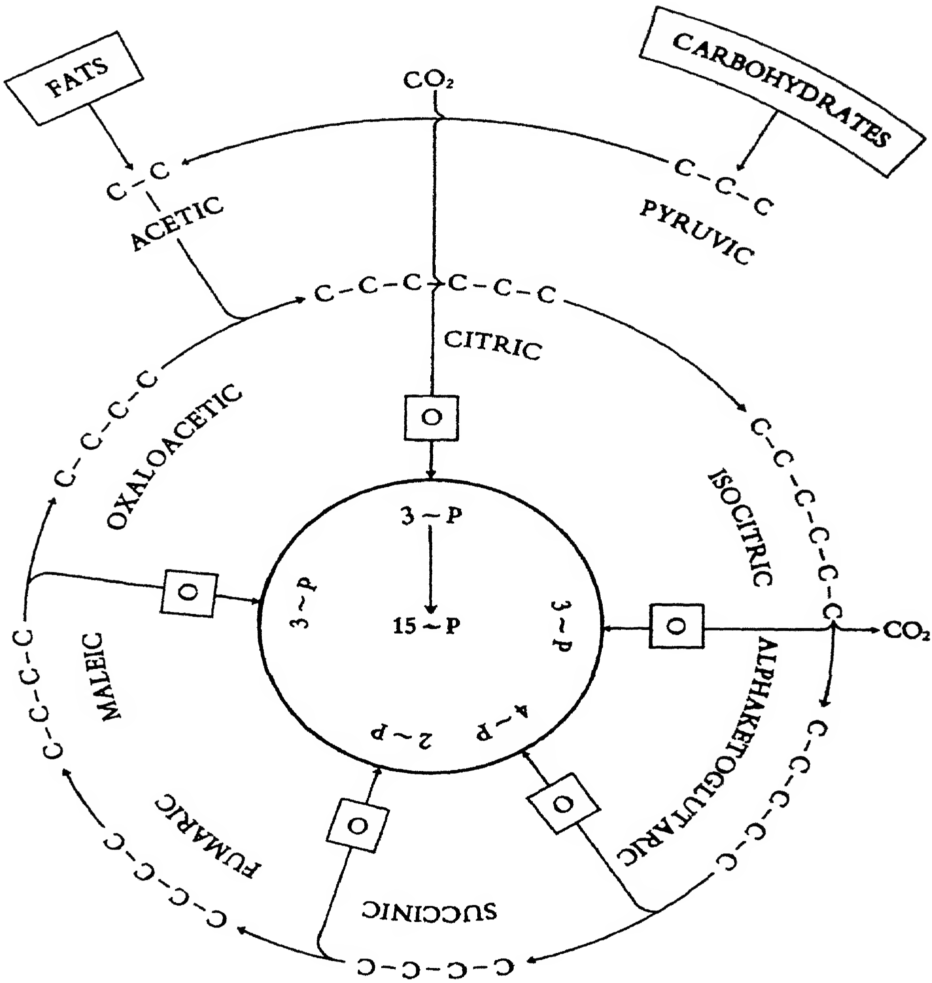
phosphate bond of ATP proceeds with extraordinary efficiency. For each molecule of glucose completely oxidised to CO_2 and H_2O in a tissue preparation, approximately 38 molecules of free phosphate and 38 molecules of ADP combine to produce 38 molecules of ATP. It has been shown that the formation of one mole of ATP from ADP in this reaction as it occurs in the cell requires about 12000 calories. The formation of 38 moles of ATP therefore required $38 \times 12000 = 456{,}000$ calories. Compared to the maximum of 690,000 calories which can be expected from the combustion of one mole of glucose, the recovery of 38 moles of ATP represents a conversion of 66% of the energy. As a comparison a modern steam generating plant converts about 30% of its energy input to useful work.

Just how the energy is transferred from fuel molecules to ATP is a problem that has preoccupied many biochemists for decades.

Investigators have broken down the labyrinthine succession of reactions into 3 major stages. In the first stage, enzymes break down the sugar and fat molecules (and protein fragments) into a simpler unit that represents a kind of common denominator of the distinctly different structures of these fuels.

The breakdown of 6-carbon glucose molecule to 2-carbon-pyruvate molecule is not so simple as it sounds. Some 40 years of intensive work went into the resolution of the details of this process and isolation of a dozen specific enzymes sequentially involved in the process.

The intermediate pyruvic acid molecules become the centre of activity in the second stage. They are converted to the 2-carbon compound acetic acid, in a combined or "activated" form with Co-enzyme A, a substance that contains pantothenic acid, one of the B vitamins. It is at this point that fats and proteins broken down to acetic acid by enzyme systems specifically adapted to their structures, also join the *common pathway* of oxidation. Another set of enzymes acting sequentially and cyclically links up acetic acid with oxalo-acetic acid, a 4-carbon compound, to citric acid, a 6-carbon compound. The second stage is often called the citric acid cycle, after this important intermediate; it is also known as Krebs' cycle in recognition of Sir Hans Krebs of Oxford University who first postulated it in 1937. As the cycle continues, the citric acid undergoes a series of rearrangements and degradations, in the course of which oxalo-acetic acid is regenerated for the next round and the two carbons from the acetic acid molecule are oxidised to form two molecules of CO_2. Half of the task of oxidation is now completed.



Citric acid cycle stores in the high-energy bonds of ATP the energy released by the oxidation of fats and carbohydrates. Each turn of the cycle makes 15 high energy phosphate bonds.

Meanwhile, during the dismemberment of pyruvic acid molecule in the citric acid cycle, intermediate compounds have picked up the pairs of hydrogen atoms that are attached to carbon-atoms. The hydrogens are carried over into the third major multi-enzyme sequence to be combined with oxygen which is brought from the lungs via circulation. This so called respiratory cycle thus yields water, the second of the two end products of the biological oxidation.

As elementary as the combustion of hydrogen and oxygen may seem, the unravelling of the chain of enzyme activity in the respiratory cycle has engaged top biochemists for fifty years, prominent among them being Otto Warburg of Germany and David Keitlin of England. The hydrogen atoms do not by any means enter directly into combination with the oxygen. They or their equivalent electrons, set free when the hydrogen is ionised, travel to this terminus along a chain of hydrogen and electron transferring enzymes in the cell. Each of these enzymes possesses a characteristic and specific "active group" that is capable of accepting electrons from the preceding member of the chain and of passing them along to the next. The chemical nature of the active groups explains why animals including man must have certain minerals and vitamins in their diet; all the groups contain either a metal such as iron or a vitamin such as riboflavin (Vit. B2). The lack of any of these essential activators may interrupt the chain and cause faulty or incomplete oxidation of food stuffs in the cell. Since the oxidation of one molecule of glucose sets 12 pairs of hydrogen atoms moving down the chain and since a pair of hydrogen atoms passing down the whole chain gives rise to 3 moles of ATP, respiratory chain generates 36 moles of ATP.

In 1948, it was shown that enzymes involved in both citric acid and the respiratory cycles are located in the mitochondria, where ATP is made by oxidative phosphorylation.

ATP has been called the energy currency of the living cell. Every sort of vital process from the contraction of a muscle to the synthesis of a hormone, draws on ATP.

At this point it may be worthwhile to consider the terms oxidation and reduction. Essentially oxidation means removing an electron from a molecule, and reduction means adding an electron. The term oxidation refers to any loss of elctrons in a chemical reaction, whether or not oxygen is involved.

Often, though not invariably, an electron travels in company of a proton, as a part of a hydrogen atom. In that case oxidation means

removing hydrogen and reduction means adding hydrogen. The concepts of oxidation and reduction are convenient ways of viewing chemical reactions, in biological systems. Here, the removal of electrons from one substance and their subsequent transfer to others is the chief means of energy release.

The human body is a chemical engine. At rest it transduces chemical energy present in food into mechanical work, as in the beating of the heart and the movements of the diaphragm and rib cage in respiration. This accounts for less than 10 per cent of the resting energy, the remainder being utilised in the osmotic pumps which maintain the ionic gradients in the tissues and in the chemical syntheses needed to replace the molecules continually broken down in the turnover of the components of the cells. All of this energy is ultimately lost to the body in the form of heat.

Cytochrome Enzymes

Biological oxidation involves at least a score of special enzymes that act first as acceptors and then as donors of the electrons or hydrogen atoms removed from food molecules. In the last part of the process one finds a series of Cytochrome molecules (identified by various subscript letters), all of which incorporate a *heme* group containing iron, the same heme group found in haemoglobin. Electrons are passed down a chain of Cytochrome molecules: from Cytochrome B to Cytochrome C_1 – Cytochrome C – A – A_3 and finally to oxygen atoms where they are combined with hydrogen atoms to produce water. This is a stepwise process designed to release energy in small parcels rather than all at once. In the transfer of electrons from Cytochrome B to C, and again in the transfer between Cytochromes A, A_3 and oxygen, energy is channelled off to synthesise ATP which acts as a general purpose energy source for cell metabolism.

To illustrate how similar all eukaryotes really are to one another, it has been found that Cytochrome C from any species of plant, animal or eukaryotic micro-organism can react in the test tube with the Cytochrome oxidase from any other species.

The primary need of the body is fuel to supply energy for the vital functions. Normally the principal fuel is glucose, and its most critical user is the brain, for which glucose is fully as essential as oxygen. A rapid drop of sugar level in the blood, which must continuously deliver glucose to the brain, brings about behavioural changes, confusion, coma, and if prolonged, structural damage to the brain resulting in

death. In the body at rest the brain consumes about *two-thirds* of the total circulating glucose supply (compared to 20 per cent of the oxygen supply). Most of the remaining third of the glucose supply goes to the skeletal muscles and red blood cells.

The human brain required between *100* and *145* gms. of glucose (equivalent to about 400 to 600 calories) per day. The body's main reserve of glucose, in the form of glycogen in the liver, amounts to considerably less than 100 grams. As a result, the liver's reserve store of fuel supply can suffice for the brain's needs for only a few hours. In fact, the stored glucose is not sufficient for the duration of overnight fast between dinner and breakfast. Between meals the liver begins to draw on the tissues of the body for materials to synthesize the required glucose. After a person has eaten a meal at 10 p.m. certain amino-acids *alanine* and *serine* that are precursors for the synthesis of glucose, begin to accumulate in the blood plasma by 1 a.m. and they continue to increase until breakfast. The rise in amino-acids is an indication that proteins in the skeletal muscles are being broken down to provide material for the production of glucose by the liver. At the same time the level of free fatty acids rises, derived from the breakdown of triglycerides in the fatty tissues; these are capable of supplying energy to tissues other than those of the nervous system. The triglycerides can also provide a source for glucose synthesis but they can furnish only about 16 grams a day.

The body cannot do entirely without glucose because most tissues need it for replenishing the tricarboxylic acid (TCA) cycle, which among other things synthesizes *ATP* on which so much of the body's chemistry depends.

Intermediary Metabolism

When food is ingested the absorptive process begins through the action of intra-luminal and brush-border enzymes in the intestine which break down complex carbohydrates, lipids and proteins to constituent sugars, fatty acids and amino-acids. The normal diet is a mixture of all three components and absorption and metabolism of carbohydrate, fat and protein occur simultaneously. For descriptive purposes, however, each is described separately.

Carbohydrates

Following a carbohydrate meal (e.g. rice) absorbed sugars pass into the portal vein for transport to the liver and peripheral tissues. A plasma glucose concentration rises, insulin release from the pancreas is

stimulated and glucagon levels fall. The magnitude of insulin response to glucose is increased through the action of other gastro-intestinal hormones secreted following food intake, the major among them being GIP (gastric inhibitory polypeptide). The newly released insulin accelerates the disposal of glucose in muscle and adipose tissue. In muscle a portion of the glucose taken up is oxidised, and the remainder is stored as glycogen. In adipose tissue (fat stores) glucose is utilised for *de novo* synthesis of long chain fatty acids, which in turn are esterified with glucose-derived glycerol to form triglycerides. In the liver, glycogen synthesis is favoured following a meal, by conversion of glucose-6-phosphate (G6P) from activation of the enzyme glycogen synthetase, and inactivation of glycogen phosphorylase.

Protein

After a protein-containing meal, absorbed amino-acids pass via portal vein to the liver. It is worth noting that amino-acids entering the systemic circulation from the liver *do not* reflect the make-up of ingested protein; about 60 per cent of the total is accounted for by the branched chain components, valine, isoleucine and leucine. The branched chain amino-acids play a pivotal role in overall protein metabolism. They are responsive to the anabolic effect of insulin on muscle, and leucine seems to have a specific stimulatory effect on protein synthesis. Probably the replenishment of protein stores in muscles following a meal is a function of branched chain amino-acid uptake. During fasting, muscle has the capacity (not shared by the liver) to oxidize the branched chain amino-acids for energy purposes as fuel.

Amino-acids during absorption stimulate insulin as well as glucagon release from the pancreas. Glucagon may prevent hypoglycemia when insulin secretion is stimulated by a protein meal under circumstances where dietary carbohydrate is absent or limited.

Fat

Fat absorption is slower than that of carbohydrates and proteins and follows a different course. Intestinal transport may take several hours to complete. Following absorption of long chain fatty acids, triglyceride is re-formed inside the intestinal cell and packaged in the form of chylomicrons that then pass into the lymphatic channels and enter the systemic circulation via the thoracic duct. During transit both in the lymph and plasma the apolipoprotein content of the chylomicron is altered by exchange with high density lipoprotein

(HDL). There is an increase in apoprotein CII, an activator of lipoprotein lipase. In the capillaries of a number of tissues, especially the adipose tissue and skeletal and cardiac muscle, the triglycerides of the chylomicrons are broken down to free fatty acids and 2-monoglycerides by lipoprotein lipase. The monoglyceride is hydrolyzed subsequently by a monoglyceridase. The free fatty acids liberated by the two reactions pass into the cell where they may be oxidised for energy purposes or re-esterified for storage as triglycerides. Most of the triglyceride in the chylomicrons is removed in a single passage through the peripheral capillary bed. The cholesterol-ester-rich remnant particle then passes to the liver where it serves to regulate hepatic cholesterol synthesis.

Insulin stimulates fatty acid synthesis and triglyceride formation in the adipocytes. Insulin is also required for the synthesis of lipoprotein lipase. It inhibits lipolysis catalysed by intra-cellular hormone-sensitive lipase.

The first few hours after meals are characterized by an anabolic state. Some substrate is utilised immediately for energy purposes, but significant quantities are stored as glycogen, structural protein, and fat to be used as needed in the post-absorptive period or during prolonged fasting.

Catabolic Phase

The brain and other parts of the central nervous system can utilize only glucose or ketone bodies for energy, hence during a fast plasma glucose concentration must be sustained in a safe range until acetoacetate and B-hydroxybutyrate concentrations rise to protective levels.

The liver plays a central and crucial role in glucose homeostasis. It breaks down its stored glycogen and it also forms new glucose (gluconeogenesis). Free fatty acids, although not themselves substrates for glucose production, provide the energy required for gluconeogenesis and also provide an alternative fuel to be utilised directly by many tissues, and to serve as a substrate for ketone body synthesis in the liver. As a result of these, after only a few days of fasting most tissues of the body utilize free fatty acids and ketones for energy, sparing glucose for the central nervous system.

All these adaptive processes are hormonally mediated. As the blood glucose level declines, there is a fall in insulin level and concomitant rise in four counter-regulatory hormones, glucagon, epinephrine,

cortisol and growth hormone.

At the level of the liver, starvation-induced fall in blood sugar leads to a fall in insulin and rise in glucagon and a resultant rise in the hepatic cyclic AMP. Break-down of glycogen begins immediately. This is accompanied by suppression of glycolysis (the oxidation of G6P to pyruvate) and stimulation of gluconeogenesis. This is achieved by control on the key regulatory enzymes of glycolysis phosphofructokinase (PFK), and pyruvate kinase. The substrates for gluconeogenesis are lactate, glycerol and amino-acids, especially *alanine* and glutamine. The advantage of alanine is its ready ability to enter the hepatocyte for the gluconeogenic pathways. While liver is the primary site of gluconeogenesis, measurable glucose production also occurs in the kidneys during prolonged fasting. The end result is that muscle protein becomes the major source of new glucose formation by the liver. The amino-acids utilized in gluconeogenesis come from structural protein of muscle rather than from non-functional storage food. Enzyme proteins, transport protein molecules and membrane proteins, all of which are vital for cellular integrity, all are sacrificed during starvation, when limitation of protein becomes critical.

Body fat represents the organism's primary defense against starvation. The average sized person has about 140,000 calories stored as fat, compared with 24000 cal. as protein and 300 cal. as glycogen. If adipose tissue is depleted because of disease or famine, fatal hypoglycemia or death from protein deficiency may occur.

The Chemistry of the Brain

Neurons share the biochemical machinery of all other living cells, including the ability to generate chemical energy from the oxidation of food-stuffs, and to repair and maintain themselves. Among the specialised features they possess and other cells do not, are those that have to do with the special function of neurons as transmitters of nerve impulses, such as their need to maintain ionic gradients, involving a high rate of energy consumption, and those associated with the ability of neurons to manufacture and release a special array of chemical messengers known as neurotransmitters. At synapses, the microscopic regions of close proximity between the terminal of one neurone and the receiving surface of another, the arrival of an impulse causes a sudden release of molecules of transmitter from the terminal. The transmitter molecules then diffuse across the fluid-filled gap between the two cells and act on specific receptor sites in the post-synaptic

membrane, thereby altering the electrical activity of the receiving neurone.

Considerable progress has been made in recent years in characterizing the various transmitter substances (over 30 have been identified so far and more may be discovered) in mapping their distribution in the brain and in elucidating the molecular events of synaptic transmission. The transmitters are not randomly distributed throughout the brain but are localized in specific clusters of neurons whose axons project to other highly specific brain regions. The superimposition of these diverse chemically coded systems on the neuronal circuitry endows the brain with an extra dimension of specificity and modulation.

The chronology of the discovery of neurotransmitters and neuropeptides in the central nervous system is given in Table II.

According to current speculation the causes of mental illness may ultimately be traced to defects in the functioning of specific transmitter systems in the brain. The basis for the speculation is the revelation that the behavioral effects of many drugs and neurotoxins arise from their ability to disrupt or modify chemical transmission between neurons.

The functional chemistry of the brain is exceedingly difficult to study. The 30-odd neurotransmitters have a characteristic inhibitory or excitatory effect on neurons. The commonest inhibitory transmitter in the brain is GABA (gamma—amino butyric acid), an amino-acid that is not incorporated into proteins. GABA is unique among amino-acids in that it is manufactured almost exclusively in the brain and spinal cord. The enzyme glutamic acid decarboxylase catalyzes the manufacture of GABA from glutamic acid. It is of interest to note that glutamic acid itself is a candidate excitatory transmitter in the brain whereas GABA, which differs from it by a single chemical group, is an inhibitory transmitter. Clearly slight differences in molecular structure of transmitters can give rise to completely different physiological effects.

The interaction of the transmitter with its receptor alters the 3-dimensional shape of the receptor protein, thereby initiating a sequence of events. The interaction may cause a neuron to become excited or inhibited, a muscle cell to contract or a gland cell to manufacture and secrete a hormone. In each case the receptor translates the message encoded by the molecular structure of the transmitter molecule into a specific physiological response. Some of the responses,

such as the contraction of voluntary muscle, take place in a fraction of a second; others, such as the secretion of a hormone, require a span of minutes and sometimes hours.

Many transmitter receptors have two functional components, a binding site for the transmitter molecule and a pore passing through the membrane that is *selectively permeable* to certain ions. The binding of the transmitter to the receptor changes its shape so that the pore is opened and ions inside and outside the cell membrane flow down their concentration gradients, resulting in either an excitatory or an inhibitory effect on the neuron's firing rate. Whether the electric potential generated by a transmitter is excitatory or inhibitory depends on the specific ions that move and the direction of their movement. Acetylcholine is excitatory at the synapse between nerve and muscle because it causes positively charged sodium ions to move into the cell and depolarize its negative resting voltage. GABA, on the other hand, has a receptor whose pore is selectively permeable to the negatively charged chloride ions. When these ions flow through the open pores into the target cell, they increase the voltage across the membrane and temporarily inactivate the cell.

Other transmitters such as dopamine and norepinephrine appear to operate by a more elaborate mechanism discovered in the mid-1950's by Earl W. Sutherland and his colleagues at Case Western Reserve University. The discovery of a *"second messenger"* cyclic AMP, that mediates the electrical or biochemical effects of the transmitter, or ''first messenger'', brought him the 1971 Nobel Prize in physiology and medicine.

According to Sutherland's hypothesis, the receptor protein for norepinephrine (and many other transmitters) is coupled in the target-cell membrane to the enzyme adenylate cyclase, which catalyses the conversion of the cellular energy-carrying molecule adenosine triphosphate (ATP) into a small molecule, cyclic adenosine monophosphate (c AMP). Cyclic AMP then acts on the biochemical machinery of the cell to initiate the physiological response characteristic of the transmitter.

The application of Sutherland's second messenger theory to brain function is one of the most exciting areas in neurochemistry. Several neurotransmitters including norepinephrine, dopamine, serotonin and histamine, act through c AMP, which in turn activates specific enzymes in the target cell called protein kinases; these enzymes then act

to catalyze the incorporation of phosphate groups into special proteins in the neuronal membrane, altering the permeability of the membrane to ions and thereby changing the level of excitability of the target cell. Because the second messenger system works relatively slowly on the time scale of neuronal events it is best suited for mediating the longer-lasting actions of transmitters in the brain such as slow shifts in membrane potentials and perhaps the formation of long term memories.

Although the study of transmitter systems in the brain have already provided major clues to the chemical mechanisms involved in learning, memory, sleep and mood, it seems clear that the most exciting discoveries lie ahead. We now have the techniques of studying the chemistry of the living human brain, with the help of positron emission tomography and NMR.

An example of the use of positron-emission-tomography in clinical neurology is in the selection of patients for surgery in the treatment of focal epilepsy. In 1980 Kuhl described the finding of localised regions of diminished Fluorine-18 deoxyglucose metabolism at the sites of origin of epileptic seizures in patients with temporal lobe epilepsy. Surgical removal of the seizure focus resulted in marked relief of seizures in previously untreatable patients. Deoxyglucose metabolism has also been found to be deranged in patients with strokes, senile dementia and Huntington's Chorea.

One of the most fundamental questions in biology is the mechanism by which physical and chemical processes within the brain determine behaviour. Related questions are how the external world is represented in the brain. It is well established that certain behaviour patterns are associated with well-defined areas of the brain. The question is whether we can identify them by measuring their biochemical activity. It is now clear that neurotransmission involving receptors is important for the normal functioning of the nervous system. Four major biogenic amines, dopamine, norepinephrine, epinephrine and serotonin are known to affect normal behaviour and psychiatric disorders such as depression. It has been postulated that the mesolimbic dopaminergic pathway is involved in schizophrenia. Cyclotron-produced radionuclides can now be incorporated into analogs of the receptors of interest. It is hoped that such studies would show regional biochemical correlates of psychological phenomena and neuro-psychiatric disorders.

TABLE I

Subcellular Localization of Enzymes

Nucleus	: DNA replicase DNA dependent RNA Polymerase NAD & NADP synthesizing enzymes Histone synthesizing enzymes
Mitochondria	: Tricarboxylic acid cycle enzymes fatty acid oxidising enzymes respiratory chain and oxidative phosphorylation enzymes. Haem synthesizing enzymes.
Lysosomes	: Deoxyribonuclease Ribonuclease Cathepsins Lipases Phosphatases Glucosidases B—glucuronidase Sulphatase Esterases
Rough Endoplasmic Reticulum (microsomes)	: Protein synthesizing enzymes
Smooth Endoplasmic Reticulum	: Phospholipid synthesizing enzymes Cholesterol synthesizing enzymes. Glucuronide synthesizing enzymes. Hydroxylases or mixed function oxidases Lipid peroxidising system
Cytosol (cell sap)	: Glycolytic enzyme system Fatty acid synthesizing system Pentose cycle enzymes Amino-acid activating enzymes
Cell boundary and limiting membranes within the cell	: Adenosine triphosphatase (ATPase) Adenyl cyclase

TABLE II

Chronology of the Discovery of Neurotransmitters & Neuropeptides in the Central Nervous System.

Year	*Transmitter*	*% of brain synapses*
1920	Acetylcholine Epinephrine	5 – 10
1940's	Norepinephrine	0.5
1950's	Amino-acids GABA Glutamic acid Aspartic acid	25 to 40
	Dopamine	0.5
1960's	Substance P	
1970	Serotonin	0.5
1974	Hypothalamic Releasing Factors TRH LHRH SRIF	
1975	Encephalin	
1976	VIP, CCK	
1977	ACTH	
1978	Other pituitary hormones, Insulin, Vasopressin, Oxytocin, Angiotensin	
1979	Glucagon	
1981	Corticotrophin releasing hormone	
1982	Growth-hormone releasing hormone	

Concentrations in the brain

Amino acids 10^{-6} to 10^{-8} moles per milligram of protein

Monoamines & AC 10^{-9} to 10^{-10} ,, ,, ,,

HRH, Gut hormones 10^{-12} to 10^{-15} ,, ,, ,,

Chapter 8

HUMAN GENETICS, ANCIENT AND MODERN

Introduction

The distinguished theoretical physicist Erwin Schrodinger has called the science of genetics "easily the most interesting of our days". No other branch of Science in the 20th Century has contributed more to man's understanding of himself and the living world in general. Genetic discoveries have provided new insights into such fundamental problems as the origin of life, the structure of the living matter and evolution. The great accomplishment of this science has been to discover the physical basis of heredity and to show that the basic rules of inheritance are fundamentally the same throughout the living world and that the genetic code is universal. The conceptual union of genetics and metabolism is perhaps the most fruitful development in biological science of the past decade. Each of these disciplines has profound explanatory consequences for the other, and both have implications for the understanding of human disease.

Genetic Concepts in Ayurveda

Among the various causative factors of disease, Charaka describes *"Beejabhagadushti"* (defect in the seed) and *"Beejabhagavayavadushti"* (defect in the components of the seed).

Ayurveda also described many congenital abnormalities, *"Janma bala pravrutta Vyadhi"* such as "Andhya" (blindness), "Badhirya" (deafness), "Mooka" (dumbness) and many anatomical defects like anal atresia. It was also appreciated that the congenital abnormalities could be either genetic in origin or may arise as a result of factors in the intra-uterine life, as seen by the following statements in *Charaka Samhita:*

"The appellation of conception is given to that union of semen, ovum and the spirit which takes place in the womb".

"The fetus is composed of the four proto-elements derived from the four sources which are the father and the mother, the food taken by the mother during the fetal life, and one's past actions. All these exist in everyone's body".

"The malformations of shape, colour and the senses are caused by the defects of the sperm, germ, by the actions in previous life, the condition of the uterus and the season, as well as the defects of the mother's diet and behaviour during gestation".

The ancient Indians also appreciated the association of *consanguinity* with increased incidence of congenital defects. Hence husband and wife should not be blood-related to each other and should *not* belong to the same *"gotra"* or family tree for at least seven previous generations.

Charaka describes the contributions made by the mother and the father to the development of the fetus. One can only wonder about the basis on which these conjectures were formulated in ancient times.

"Those parts which pass from the mother to embryo during its formation are the blood, flesh and fat, the umbilicus, the heart, liver, spleen, kidneys, bladder, pelvic colon & stomach".

"Those parts which pass from the father to the embryo are the hair of the head and beard, nails, teeth, hair of the body, bones, veins, sinews, arteries & semen".

"In this manner, this embryo comes into existence from the coming together of those various procreative factors like a tent from the assemblage of various materials, or like a chariot from the combination of various parts of the chariot".

The following interesting question is raised by the pupils of Charaka: "If man is the offspring of man, then why are those sprung of the idiotic, the blind, the mute, the hunch-backed, the dwarfs, *unlike* the parents?"

Charaka answers the query thus:

"Only that limb or organ of the body becomes defective, whose original representative part in the spermoplasm has been rendered defective. If there is no potential defect there is no manifest deformity either".

"If again, only a part of the germ-plasm is vitiated, then the female gives birth to a *"Puti praja"* (defective progeny).

"The physician of large understanding requires to know both these sets of factors, viz. those which are helpful in the formation and

development of the fetus and those which are inhibitive of such formation and growth''.

In 1970, Hargobind Khorana successfully synthesized a gene, and in the 1980's recombinant DNA technology has come to the doorstep of the patient. We have indeed come a long way starting from the concept of ''Beej bhaga dushti''.

Experimental Tools of Genetics

Although our main interest is in human genetics, man is far from an ideal organism in which to study genes. His life cycle is too long, his offsprings are too few, his choice of mate is not often based on a desire to contribute to the knowledge of heredity, and it is inconvenient to subject him to a complete chemical analysis. As a result, most of what we learned about genes has come from studies of such diverse organisms as the garden peas, Indian Corn Plants, the mould Neurospora, the fruit fly drosophila, and bacteria and viruses.

The red mould on the bread, Neurospora, has many advantages in the study of what genes do. It has a short life cycle—only 10 days from one sexual spore generation to the next. It multiplies profusely by asexual spores; the result is that any strain can be multiplied a million-fold in a few days without any genetic change. Each of the cell nuclei that carry the genes of the bread mould has only a single set of genes instead of a duplicate set found in human cells. This means that recessive genes are not hidden by their dominant counterpart.

Study of mutant genes in Neurospora, produced by X-rays, has helped scientists to form the important concept that genes control enzymes and metabolism.

The fruit fly Drosophila melanogaster provides an excellent tool for geneticists. It can be bred easily and rapidly in the laboratories, and it has a large number of bodily traits and functions that can be easily observed. Mutations can be artificially produced by exposure to X-rays and alterations produced in identifiable morphological traits such as colour of the eyes can be compared with alterations produced in the chromosomes. The chromosomes in the salivary gland of Drosophila are large and easy to ''read''.

Evolution is generally so slow a process that during the few centuries of recorded observations man has been able to detect very few evolutionary changes among animals and plants in their natural habitat. Today, however, we can study and even produce evolutionary changes at will, in a short period, in the laboratory. *Escherichia Coli,* an

organism which grows harmlessly in the normal human intestine, is a useful organism that divides in a culture medium every 20 minutes. If several billion E. Coli are placed on a streptomycin-containing medium, a few cells will survive, and reproduce—a streptomycin-resistant mutant is thus bred. The frequency of mutants is one per billion in every generation. Streptomycin does not induce the mutation, it only enables selective growth of the mutant.

In 1915, Twort and d'Herelle independently showed that bacteria themselves were subject to attack by viruses. The bacterial viruses, called *bacteriophages,* have since then been extensively studied. In 1952 Hershey and Chase found that radioactive phosphorus taken up by virus-infected bacteria was incorporated in the new generation of viruses while radioactive sulphur was not. Phosphorus is a component of nucleic acid, and sulphur a component of protein, but not of nucleic acid. The impact of this discovery was dramatic. Nucleic acid was suddenly "in", and protein was "out", in the thinking about nature of gene action. In 1953, by ingenious experiments with bacterial viruses Crick established that the "letters" in the genetic code are read off in simple sequences and that "words" in the code consist of groups of 3 letters or triplet codons. The T4, ϕx 174, and lambda bacteriophages have become favourite experimental tools of microbial geneticists and molecular biologists. Within the space of a day or two, the geneticist working with bacteriophages can grow and study more specimens than the fruit-fly geneticist could study in a life-time. An operation as simple as the mixing of two bacterial cultures on a few agar plates can provide information on a billion or more genetic interactions in which genes recombine to form those of a new generation.

Since the genetic code is universal, a lot of exciting basic information relevant to humans has been obtained from the genetic code of the tiny ϕx 174 virus.

Viruses have proved invaluable to molecular biologists interested in the structure and function of genes. The viral genome consists of a single nucleic acid which may be either DNA or RNA (but not both). In viruses, these substances can be studied in isolation and it was such studies that led molecular biologists to some of their greatest discoveries in the 1950's and 1960's. Viral multiplication involves the controlled expression of a small number of genes and the assembly of a small number of proteins into a highly organized structure. The study of viruses in the last decade has in effect become the study of basic life processes. The assembly of viruses has become the paradigm for the

construction of large molecular structures within the living cells.

The protein coat of tobacco mosaic virus (TMV) has been studied in great detail. Chemicals like nitrous acid have been used to produce mutations in viral RNA. A change in the viral coat protein sequence resulting from such mutations changes the antigenecity of the virus. Such spontaneous mutations in the influenza virus frustrate the attempts of production of useful vaccines against that infection.

Evolution of Modern Genetics

In 1859 Charles Darwin published his book "Origin of Species". Darwin argued that all living forms are related to life in the past, from which they have evolved by slow change. Darwin also argued for the basic mechanism of natural selection. He pointed out that if every species produced more young than can survive to reproduce, some types survive more often or are more fertile than others, and if the factors determining viability and fertility are to some extent hereditary, then natural selection is a direct consequence.

The theory of evolution by natural selection must rank with the greatest contributions of human intellect. The exciting (or, to some, repugnant) discovery that man is a part of nature and shares a common ancestry with the corn plant, the earthworm and the apes has totally altered man's view of himself and of his place in the world.

The missing element in Darwin's concept of the evolution of man was a knowledge of the nature of heredity and variation; this was supplied by Mendelian genetics.

Mendel's Laws

In 1865, in the garden of a monastery near the village of Brünn in what is now Czechoslovakia, Gregor Johann Mendel, a farmer turned priest, was spending his spare time in experimenting on garden peas, studying hybrids between edible varieties of yellow and green peas, tall and dwarf plants, to understand the rules of inheritance. He found out that when a plant bearing smooth yellow peas is mated with one bearing wrinkled green peas, in the first generation of the offspring the plants bear only smooth yellow peas. In the next generation, the plants bear smooth yellow, wrinkled yellow, smooth green and wrinkled green in approximate ratios of 9:3:3:1.

Mendel's great achievement was to recognize that the random separation and reuniting of pairs of inheritance-determiners in the

germ cells would provide an orderly explanation of the seemingly unsystematic results of his cross-breeding experiments. Mendel conceived of discrete factors that determined transmission of hereditary traits and he conceived of the rules by which these were transmitted.

The essence of Mendel's discovery was that hereditary traits – or "characters" – are independent of one another and each is transmitted as a separate unit from a parent to the offspring. in other words, the organism is a mosaic of distinct and independent qualities. The units of inheritance are distributed in families and populations according to the laws of independent events, that is, the laws of chance. This view contrasted with the older idea that the characteristics of the parents are *blended* in the offspring, as one might blend two liquids by mixing them together (a misconception which still persists in the expressions "full blooded", "half-blood" and the like). Mendel showed that there is no blending or dilution of individual characters in a hybrid. The expression of a given character may disappear, but the hybrid carries the character as a "recessive" unit and it may emerge in later generations. Mendelian inheritance is essentially atomistic, the heritable qualities of the organism behaving as if they were determined by irreducible particles (later on designated as *genes*). Mendel had no idea of the size, composition or location of these hypothetical particles; his main concern was with showing that inheritance can be understood in these terms, and with working out the rules of transmission of traits.

An individual is composed of thousands of heritable characters. Each character may take one of several possible forms. For instance, there are three principal forms, called A, B and O of a gene for human blood type. Every person carries a pair of genes, the possible combinations being AA, AO, BB, BO, AB and OO. A and B are "dominant" and O is "recessive" to them, so that the blood of a person with the combination AO will show the properties of the blood group A. The same is true for BO.

Mendel's paper was published in 1865 but it was totally ignored. It was not until 1900 that Mendel's principles were re-discovered, and his place in biological history was recognized. Investigators soon showed that the Mendelian rules of inheritance applied to animals as well as plants.

The Mendelian theory led to a new understanding of the biological significance of sex. It showed that the sexual method of reproduction provides an elaborate lottery which serves the function of recombining genes in new ways.

As soon as Mendel's laws became widely known, the striking parallelism between the behaviour of chromosomes, as seen through the microscope, and of Mendel's factors, as inferred from breeding experiments, immediately became apparent. Thus, the chromosomal theory of heredity had its origin shortly after the rediscovery of Mendelism in 1900.

Genes and Chromosomes

The next step was to show how genes are arranged on the chromosomes. They were found to be in single file. The fruit fly, Drosophila melanogaster provided an excellent experimental tool for the study of genes on chromosomes.

The crucial experiments done by T. H. Morgan and his students were remarkable for their ingenuity and for the simplicity of the experimental materials. To infer the position of the genes, which could not be seen and whose nature was totally unknown, solely from the numbers of different kinds of progeny from different matings seems almost impossibly abstract; yet this group was able to construct chromosomal maps giving the exact order and relative distances apart of the genes. At first the evidence was mainly the internal consistency of the chromosomal maps and the accuracy of predictions made from them. Considerably later, after appropriate techniques had been developed, the gene order was confirmed by direct microscopic examination of broken chromosomes which showed the correspondence between a missing chromosome region and missing or altered hereditary trait.

Concept of Mutations

Mutations arise from time to time in all organisms, from viruses to man. The frequency of any specific mutation is usually low. In men, according to estimates by Haldane in England and James Neel in the U.S. mutations that produce certain hereditary diseases such as haemophilia and thalassaemia, arise in one in 2500 to one in 100,000 sex cells (sperms or ova) in each generation. In drosophila and in the corn plant, the frequency of mutations ranges between 1 in 100,000 and 1 in million per generation. From this it may appear that man is more mutable than flies and bacteria, but it should be remembered that a generation in man takes some 25 years, in flies two weeks and in bacteria 20 minutes. The frequency of mutations per unit of time is actually greater in bacteria than in man.

In all organisms the majority of mutations are more or less *harmful.* If mutations produce incapacitating changes, how can adaptive evolution be compounded of them? The answer is that a mutation that is harmful in the environment in which the species or the race lives may become useful, even essential, if the environment changes, as we saw in the example of E.Coli grown in culture to which streptomycin is added. If no mutations occur in a species, it can no longer become adapted to changes and is headed for eventual extinction. Mutations arise at random, regardless of whether they will be useful at the moment, or ever; nevertheless they make the species rich in adaptive possibilities.

To understand the mechanism of mutations we must first recapitulate the molecular basis of gene expression.

Molecular Basis of Gene Expression

Each chromosome contains hundreds and probably thousands of different genes, and as many as 30% differ from one individual to another.

All hereditary information is transmitted from parent to offspring through the inheritance of specific molecules of deoxyribonucleic acid (DNA). A gene represents the total sequence of bases in DNA that encodes the amino-acid sequences of a single polypeptide chain of a protein molecule (see the chapter on 'Chemistry of Life').

Genetic information encoded in the DNA of the chromosome is first transcribed into a ribonucleic acid (RNA) copy. During transcription the ribose nucleotides align themselves along the DNA according to base-pairing rules. Thus adenine of DNA pairs with uridine of RNA, cytosine pairs with guanine, thymine pairs with adenine and guanine pairs with cytosine. The ribose bases are joined together by the enzyme RNA polymerase. The resulting RNA transcript forms the template for translation into the amino-acid sequence of a protein. Table I shows the DNA and mRNA code words for each of the 20 amino-acids in protein. The genetic code is said to be "degenerate" because certain amino-acids are specified by more than one codon.

The DNA of many genes is fragmented into discrete coding regions (exons) separated by non-coding regions (introns); these introns act as spacers between the coding regions; they are not translated into proteins. The RNA transcript is edited in the nucleus before it passes into the cytoplasm. In the editing process the intervening sequences are excised and the coding regions are spliced together to form one continuous gene.

TABLE I
The Genetic Code

1st POSITION	2nd POSITION: U	C	A	G	3rd POSITION
U	PHE	SER	TYR	CYS	U
	PHE	SER	TYR	CYS	C
	LEU	SER	CT-1	CT-3	A
	LEU	SER	CT-2	TRY	G
C	LEU	PRO	HIS	ARG	U
	LEU	PRO	HIS	ARG	C
	LEU	PRO	GLN	ARG	A
	LEU	PRO	GLN	ARG	G
A	1LU	THR	ASN	SER	U
	1LU	THR	ASN	SER	C
	1LU	THR	LYS	ARG	A
	MET	THR	LYS	ARG	G
G	VAL	ALA	ASP	GLY	U
	VAL	ALA	ASP	GLY	C
	VAL	ALA	GLU	GLY	A
	VAL	ALA	GLU	GLY	G

Explanations for the Abbreviations in Table I

1.	ALA	=	Alanine
2.	ARG	=	Arginine
3.	ASN	=	Aspargine
4.	ASP	=	Aspartic acid
5.	CYS	=	Cysteine
6.	GLN	=	Glutamine
7.	GLU	=	Glutamic acid
8.	GLY	=	Glycine
9.	HIS	=	Histidine
10.	ILU	=	Isoleucine
11.	LEU	=	Leucine
12.	LYS	=	Lysine
13.	MET	=	Methionine
14.	PHE	=	Phenylalanine
15.	PRO	=	Proline
16.	SER	=	Serine
17.	THR	=	Threonine
18.	TRY	=	Tryptophane
19.	TYR	=	Tyrosine
20.	VAL	=	Valine

$$\left.\begin{array}{l} \text{CT1 = UAA} \\ \text{CT2 = UAG} \\ \text{CT3 = UGA} \end{array}\right\} \begin{array}{l}\text{punctuation to} \\ \text{terminate the chain}\end{array}$$

AUG = Start signal

The edited RNA, which is called the *messenger RNA* (mRNA) leaves the nucleus and on entering the cytoplasm, becomes associated with ribosomes and thereby serves as a *template* for the ribosomal synthesis of proteins, with the help of *transfer RNAs.* Each transfer RNA (tRNA) contains a sequence of purine and pyramidine bases that is complementary to a specific codon in the mRNA. Those tRNA molecules with their attached amino-acids line up along the mRNA molecule in precise order dictated by the mRNA code. Under the action of a variety of cytoplasmic enzymes (initiating factors, elongation factors and termination factors) peptide bonds are formed between the various amino-acids, and the completed protein is released from the ribosome.

Mutations are stable, heritable alterations in DNA. Although the causes of mutations in humans are largely unknown, a variety of environmental agents such as radiation, viruses and chemicals are known to be mutagenic. Mutations can involve a visible alteration in structure of a chromosome, such as deletion or translocation, or they can involve a minute change in one of the purine or pyramidine bases of a single gene. This can be best illustrated by the group of diseases known as Haemoglobinopathies.

Inherited Haemoglobinopathies

Genetics, as the biochemist sees it, is largely concerned with the synthesis of proteins, whether these be the quantitatively important body constituents such as haemoglobin, the equally vital regulatory proteins – enzymes and hormones – or others including immunoglobulins and binding proteins such as transferrin. Genetically determined differences among individuals are thought to stem from differences in *structure* of specific proteins, or in the *rates* at which they are produced.

The properties of any protein are determined by the number, identity, and sequence of its amino-acid residues. A change in a single nucleotide within a codon will specify a different amino-acid. Thus a change in a single purine base in the codon which specifies the sixth amino-acid of the beta chain of haemoglobin (G*A*A ⟶ G*U*A, glutamic acid ⟶ Valine) leads to the abnormal sickle cell haemoglobin. Such a change constitutes the simplest – and presumably therefore the most probable type of genetic mutation. Such a "point mutation" accounts for most of the inherited abnormalities of haemoglobin (see Table II).

Rarely, two amino-acid substitutions occur in a single polypeptide chain, as in Hb C Harlem. Presumably, the two independent mutations

occurred within the same gene (a gene is that portion of a strand of DNA that determines the structure of a single polypeptide).

In a few abnormal haemoglobins (e.g. Hb Freiburg and Hb Gun Hill) amino-acid residues are actually missing from a polypeptide chain. This type of abnormality can be accounted for by loss of a segment of DNA ("deletion" of part of the gene), presumably as a result of non-homologous crossing-over of chromosomes.

Hereditary persistence of fetal haemoglobin is an interesting anomaly that can be explained by deletion of two closely linked genes (those for the beta and delta chains). Persons homozygous for this condition synthesize neither of the two normal haemoglobins of the adult (A and A2), and their haemoglobin is exclusively fetal in type. Such a haemoglobin does not facilitate the growth of the malaria parasite within the red blood cell, hence it is speculated that in regions where malaria was endemic, carriers of such a gene have had survival advantage.

The haemoglobins Lepore, Miyada and P – Congo are fascinating, because they contain portions of both the normal delta and beta chains. Their production can be explained by the loss of DNA from segments of adjacent genes, with formation of a "fusion" gene.

The thalassemias are disorders of haemoglobin synthesis in which one or the other polypeptide chain of haemoglobin is *produced at a retarded rate.* Those chains which are produced have a normal structure. Probably there is *insufficient messenger RNA.*

The clinical manifestations of the haemoglobinopathies are determined by both quantities and properties of the molecules produced. The properties in turn are related to the structure of the polypeptide chains. To each of the four globin chains is attached a "haem" group, a porphyrin ring structure containing an atom of iron. The major function of the globin chains and the haem rings is to adjust the environment of these four iron atoms so precisely that they can reversibly combine with oxygen under normal physiological conditions. In addition, the particular fashion in which the globin chains and their haem rings are bonded together lends unusual stability to the molecule. Oxygenated haemoglobin has one steriochemical conformation called R or "relaxed". Deoxyhaemoglobin has another, called T or "tense", because of extra intramolecular bonds which form and bind the alpha chains together more tightly than in the R state. The T conformation is further stabilised by 2, 3 diphosphoglycerate, an organic ion present

Table II

Clinical Manifestations Associated with Some Abnormal Hemoglobins

Disorder	*Abnormal Hb*	*Structural Change*	*Comments*
HEMOLYTIC ANEMIA	H	alpha$_2$ beta$_2$ – beta$_4$	Unstable hemoglobin occurring in some forms of alpha-thalassemia, precipitation of hemoglobin and hemolysis are accelerated by certain drugs.
	S	beta 6 glu – val	Forms molecular aggregates when deoxygenated, producing sickle cell anemia in homozygotes.
	C	beta 6 glu – lys	Low solubility lessens plasticity of red cells, causing hemolytic anemia in homozygotes.
	E D_{Punjab}	beta 26 glu – lys beta 121 glu – gln	Mechanisms unknown
	Zurich	beta 63 his – arg	Unstable hemoglobin precipitated by certain drugs, producing hemolytic anemia in heterozygotes
	Torino Bibba Savannah Genova Hammersmith Bristol Christchurch Shepherds Bush Boras Santa Ana Sabine Köln Casper Wien	alpha 43 phe – val alpha 136 leu – pro beta 24 gly – val beta 28 leu – pro beta 42 phe – ser beta 67 val – asp beta 71 phe – ser beta 74 gly – asp beta 88 leu – arg beta 88 leu – pro beta 91 leu – pro beta 98 val – met beta 106 leu – pro beta 130 tyr – asp	Unstable hemoglobin causes congenital nonspherocytic hemolytic anemia in heterozygotes; precipitated hemoglobin tends to form inclusion bodies within red cells, under certain conditions.
CYANOSIS due to methemoglobinemia	M_{Boston} M_{Iwate} $M_{\text{Saskatoon}}$ $M_{\text{Milwaukee}}$ $M_{\text{Hyde Park}}$ Freiburg	alpha 58 his – tyr alpha 87 his – tyr beta 63 his – tyr beta 67 val – glu beta 92 his – tyr beta 23 val *deleted*	Methemoglobin causes cyanosis in heterozygotes; some also have evidence of hemolytic anemia
CYANOSIS due to increased deoxyhemoglobin	Kansas	beta 102 asn – thr	Decreased oxygen affinity of hemoglobin causes cyanosis in heterozygotes.
POLYCYTHEMIA	J_{Capetown} Chesapeake Olympia Malmo Kempsey Yakima Hiroshima Rainier Bethesda	alpha 92 arg – gln alpha 92 arg – leu beta 20 val – met beta 97 his – gln beta 99 asp – asn beta 99 asp – his beta 145 his – asp beta 145 tyr – cys beta 145 tyr – his	Increased oxygen affinity of hemoglobin hinders release of oxygen to tissues, causing compensatory polycythemia in heterozygotes
ANEMIA due to suppressed erythropoiesis	Seattle Yoshizuka	beta 76 ala – glu beta 108 asn – asp	Decreased oxygen affinity of hemoglobin enhances release of oxygen to tissues and inhibits production of erythropoietin
HYDROPS FETALIS	Barts	alpha$_2$ gamma$_2$ – gamma$_4$	Unstable hemoglobin with high oxygen affinity occurring in high concentration in stillborn fetuses with homozygous alpha-thalassemia.

in high concentration within red blood cells which can bind together the beta chains of deoxyhaemoglobin.

If these precise steriochemical relationships are disturbed, abnormal oxygen binding and decreased stability may result. Three examples may be cited.

In alpha thalassemia, insufficient alpha chains are produced, and a relative excess of beta chains accumulate and form tetramer B4 or Hb H. Although the beta chains are individually normal, the structure of the molecule is deranged. Hb H has an abnormally high affinity for oxygen which cannot be released to the tissues. The haemoglobin is not only physiologically useless but is very unstable, tending to precipitate within the red cells and cause their premature destruction.

In haemoglobins Rainier and Bethesda, bonds which normally stabilize the T conformation of deoxyhaemoglobin can no longer be formed. As a result, the R conformation becomes a more favoured state: at any given oxygen pressure Hb Rainier will be more oxygenated than HbA.

Inherited Enzyme Defects

Sir Archibald Garrod, in 1908 published his historic series of lectures on "Inborn Errors of Metabolism". As early as 1902, Garrod suggested that the disease called alkaptonuria was transmitted as a single recessive Mendelian trait, a hypothesis that has since been thoroughly proved. Alkaptonuria is an example of a hereditary enzyme deficiency.

An enzyme performs its catalytic function by binding a molecule of some substrate compound, plus on occasion another atom or group of atoms, to "active sites" on its own intricately structured protein chain. The binding, it is thought, distorts the substrate molecule in such a way that it loses part of its substance; alternatively, by forcing it into a particular spatial relationship with another atom or radical, the enzyme causes the two to join together. The presence of electrical charges on the active sites may also play a part in these transformations. In this manner the enzyme quickly mediates a chemical reaction which in its absence, and at the moderate temperatures, pressures and concentrations typical of living organisms, would take place very slowly or not at all.

A change in even one of the amino-acid residues that make up the enzyme molecule could render it structurally incapable of performing its catalytic function. But not every change is a catastrophic one. Like the

haemoglobin molecule, enzymes can undergo considerable variation without completely losing their functional properties. In fact, different organs of the body are known to produce "isoenzymes"—enzymes that are chemically slightly different but functionally identical, or at any rate identical enough to do the same chemical job in the same way.

If, however, the enzyme molecule is changed too radically by a genetic mutation, or if it is not produced at all, catalysis cannot take place. In most hereditary enzyme defects we do not, as a matter of fact, know whether the enzyme is structurally inadequate or missing altogether. Nearly all our enzyme tests are purely functional ones, showing only that the enzymatic reaction in question is or is not proceeding at a normal rate, but not why. The result of lack of enzymatic activity is either a build-up in body levels of the substrate, or a deficiency in the product of the enzymatic reaction, or a combination of the two.

This picture of enzyme function helps explain why most hereditary enzyme disorders are "recessive" conditions, that means they need the *pair* of defective genes to manifest themselves. Heterozygotes, with one defective and one normal gene, do in fact show a reduction in the body enzyme levels to something like 50 per cent of normal, but even this reduced level is adequate under most conditions to avert pathological consequences, since a single enzyme molecule can process upto 100,000 molecules of the substrate every minute.

The example of phenylketonuria will illustrate these broad generalities very well.

Phenyl Ketonuria (PKU)

This condition was described in 1934. when the Norwegian clinician A. Folling reported ten patients, several of them siblings, who had the characteristic combination of severe mental retardation, and excessive excretion of phenylpyruvic acid in the urine. Large quantities of the amino-acid phenylalanine accumulate in the body as a result of the body's failure to oxidise dietary phenylalanine to another amino-acid tyrosine. The failure in turn is caused by inactivity of the liver enzyme phenylalanine hydroxylase, which normally presides over this oxidative reaction.

The major pathologic effect of these metabolic abnormalities is interference with the development of the central nervous system during early childhood, resulting in severe mental retardation.

Simple techniques have now been developed for early case finding such as testing the new born baby's napkin (urine-contaminated) for evidence of PKU and testing the cord blood for excess phenylalanine.

A rational therapy would be to *restrict* the intake of phenylalanine in the baby's food. Since phenylalanine is essential for the formation of body proteins, its complete elimination from the diet would clearly interfere with growth. Hence present practice is to lower the intake of the amino-acid to amounts needed for normal growth. The actual criterion is provided by blood assays; levels are held to slightly above normal phenylalanine level (about 2 mg %).

Today more than 120 diseases are recognized due to genetically determined deficiency or inactivation of enzymes. In future it may be possible to enclose enzymes and co-enzymes in tiny semi-permeable polymer beads which would allow substrate to diffuse in and the product to diffuse out; the beads could be introduced directly into the blood stream where they might remain active for a long time.

Phenylalanine $CH_2CHCOOH$ (NH_2) ⟶ Phenyl pyruvic acid Excreted in *PKU*

↓ Phenylalanine Hydroxylase

Tyrosine OH CH_2CHOOH (NH_2) $\xrightarrow{\text{Tyrosinase}}$ Melanine polymer absent in *Albinism.*

↓

pOH phenyl pyruvic acid OH CH C-COOH (O)

↓ Phenyl pyruvic oxidase ⟶ Excess p-OH Phenyl pyruvic acid excreted in *scurvy* (Vitc def)

Homogentisic acid HO OH CH_2COOH

↓ Homogentisic acid oxidase ⟶ Excess Homogentisic acid excreted in *Alkaptonuria*

Maleylaceto acetic acid OH COOH C – OH CHCOOH

Study of Human Chromosomes

Human Chromosomes were visualised as early as 1880. The earliest known renderings of human chromosomes were the drawings based on observations in dividing nuclei from epithelium, published in 1882 by the German microscopist Walter Flemming.

The year 1956 was a milestone in human cytology, for it was then that J. H. Tjio and Albert Levan achieved the first accurate count of human chromosomes. The basic process by which chromosomes are identified and studied is called karyotyping. The first step is to culture human cells of some sort—usually peripheral blood lymphocytes, because they are easily obtained. Under the stimulus of a plant lectin called PHA (phyto-haemagglutinin) such cells will divide; the addition to the culture of a compound such as colchicine arrests the cell division at metaphase, when the chromosomes are discrete and easily visible. Placed in a hypotonic salt solution, the cells absorb water and swell, thereby spreading the chromosomes apart from one another, so that they can be clearly distinguished. The preparation is then fixed, stained and photographed.

The x-shaped objects of different sizes that one sees in such preparations are in fact double chromosomes, united only at the centromere; had division been allowed to proceed, they would shortly have split at that point, forming two complete sets of normal single chromosomes for the two daughter cells.

Based on the length, and the position of the centromere, seven groups are formed to identify the 22 pairs of autosomes and the two sex chromosomes X and Y. Within groups some pairs can be distinguished from each other morphologically e.g. by location of their centromeres; or by autoradiographic demonstration of early or late DNA synthesis in the cell cycle; the late replicating X chromosome of the female can thus be observed to be heavily labelled; renaturation and denaturation of the short chain repetitive DNA yields specific staining of centromeres, secondary constrictions and the long arm of the Y chromosome: The X chromosome and the autosomal pairs 6, 7, 8, 10 and 12 cannot be differentiated by this technique. Specific staining of the bands of chromosomes, including most of the long arm of the Y, with the fluorescent dye quinacrine is another useful technique. In the third, most useful technique, chromosomes are treated either by changes in pH or with proteolytic enzymes such as trypsin; specific regions of each chromosome can then be stained with Giemsa and banding patterns for each arm of each chromosome that are typical for

only that chromosome can be observed. Such precise identification enables us to characterize chromosomal abnormalities more accurately.

Mapping of Human Chromosomes

So far the existence of more than 800 human gene loci has been established and another 1000 loci have been identified tentatively, on particular chromosomes. Almost 80X-linked genes (e.g. colour blindness, haemophilia) are now located. Having placed loci on a particular chromosome, one is in a position to try to estimate their relative location on that structure. The mapping of autosomes is a much more difficult task than X chromosomes. Pedigree studies, studying the electrophoretic variants, and phenotypic expressions of disease, have helped in mapping the human genes. It has now become possible to establish gene banks or libraries for each chromosome. This work is advancing rapidly with an enormous potential impact on future medical research and an understanding of human biology. Probably the mapping of the entire human genome may be achieved during the next decade.

Clinical Spectrum of Genetic Diseases

Human disease has to be considered as an outcome of the interaction between an individual's genetic make-up and environment. In certain diseases, however, the genetic component is so overwhelming that it expresses itself in a predictable manner without a requirement for extraordinary environment. Such diseases are termed "genetic disorders".

In thinking about the role of genetics in disease it is useful to view disease in three categories. Some disorders are determined primarily by a single locus, and follow the Mendelian laws of inheritance (autosomal dominant and recessive, X-linked dominant and recessive).

Other disorders have a numerical or structural abnormality of the chromosomes of the relatively gross sort that can be detected by presently available methods.

Most of the other disorders are multifactorial. They tend to run in families but do not show the simple Mendelian pedigree pattern typical of the first category. Environmental and genetic factors, both usually multiple, collaborate in their causation. Essential hypertension, obesity, diabetes mellitus, peptic ulcer, coronary artery disease, and many congenital malformations such as cleft-lip and palate, fall in this

category. In animal experimental models, by selective inbreeding it has become possible to produce all the above-mentioned diseases in a predictable form. Hopefully these models will provide a better understanding of the precise genetic mechanisms involved.

This three-way categorization is to some extent arbitrary. The single gene disorders are influenced by other genes and by the environment, and all are, therefore, to some extent multifactorial. Chromosomal aberrations could be viewed as polygenic. Even in the multifactorial disorders the influence of a single gene locus can often be identified. However, the classification has practical usefulness because the approach to the study of the three types differs. Genetic counselling differs too, according to the category.

Since the late 1950's medical genetics has experienced a marvellous integration of previously largely separated strands: cytogenetics, biochemical genetics, pharmacogenetics, bloodgroup genetics, immunogenetics and statistical-formal-population genetics.

Treatment Possibilities in Genetic Diseases

A better understanding of the basic pathophysiology permits a variety of therapeutic approaches in the management of genetic disorders. In theory a genetic disease due to an enzyme deficiency can be managed by correcting the biochemical abnormality, by correcting the enzyme defect or finally by correcting the gene defect, the dream of genetic engineering. In practice at present, only the biochemical correction is feasible. Some management approaches currently employed are listed in the next section.

TYPES OF TREATMENT IN GENETIC DISEASES

1. **Elimination diets**

galactosemia	— galactose
phenyl ketonuria	— phenylalanine
Refsum's disease	— phytanic acid

2. **Dietary Supplements**

Orotic aciduria	— uridylic & cytodylic acids

Combination of 1 and 2

Homocystinuria	— low methionine diet, supplemental cystine

3. **Avoidance of drugs**

porphyria	— barbiturates
G6PD deficiency	— primaquin & other oxidant drugs
Cholinesterase deficiency	— muscle relaxants like succinyl-choline

4. **Accelerate excretion from body**

Haemochromatosis	— iron: by dexferrioxymine
Wilson's Disease	— copper: by penicillamine
gout	— uric acid: by benemid

5. **Replacement of gene products**

Haemophilia	— Anti-haemophilic globulin (AHG)
Agammaglobulinemia	— gamma globulin
Dyshormonogenesis of Thyroid hormone	— Thyroxine
Pituitary dwarfism	— Growth Hormone

6. **Replacement of defective tissue**

Thalassaemia	— Bone marrow transplant
Hereditary nephritis	— Kidney transplant
Cystinosis	— Kidney transplant

7. **Surgical treatment of other forms**

Hereditary spherocytosis	— Splenectomy
Peutz Jegher's syndrome	— Polypectomy
Retinoblastoma	— Eye removal
Glycogen storage disease	— Portacaval shunt to bypass liver

8. **Prevention of Complications**

Rh desensitization	— in Rh-negative pregnant female
Surgical removal of colon	— in polyposis, to prevent malignancy
Cystic fibrosis	— antibiotics for respiratory infection

9. **Competitive inhibition**

Oxalosis	— glyoxalate—oxalate

10. **Modification of metabolic pathway**

Congenital adrenal hyperplasia	— corticosteroids

11. **Enzyme replacement**

Mucopolysaccharidosis	— lysosomal enzyme replacement via plasma or leucocytes

12. **Enzyme induction**

Crigler Najjar syndrome	— enzyme glucuronyl transferase induced by drug phenobarbitone

Genetic Counselling

Our understanding of genetic disease has expanded enormously in the past 30 years, but the proportion of cases where this understanding has led to a successful approach to treatment is still very small. This means that if we are to aim at reducing the amount of ill-health caused by deleterious genes, we must aim at avoiding their transmission, rather than reversing their effects. The expanding list of known genetic abnormalities, more accurate knowledge of their modes of inheritance, and the employment of new investigative techniques, together enable us to predict with increasing accuracy the probability that a particular couple will produce an abnormal infant, and thereby reduce the likelihood that such an infant will be born or even conceived. It is thus an important area of preventive medicine.

It is essential to define a number of terms that are frequently confused by laymen and occasionally by doctors. These are congenital, genetic, hereditary and familial.

Congenital literally means present at birth. Such conditions may be environmentally caused, e.g. maternal rubella, thalidomide-like drugs. Others may be genetic i.e. caused by an abnormality of a single mutant gene or by an excess, deficiency or rearrangement of the chromosomes which may involve large number of genes. Others, of course, result from an interaction of genetic and environmental factors.

Some genetic diseases are congenital, others are not. Huntington's chorea is a notorious example of a genetic disease manifesting itself

only when the individual is well into adult life. A recent example is idiopathic hypertrophic subaortic stenosis, a type of heart disease easily diagnosed now by ultrasonography.

A *"familial"* disease is simply one that "runs in families". It can be caused by defective genes, or by a common environment shared by all members of the family (such as exposure to tubercle or lepra bacilli).

Chromosomal abnormalities are genetic in the sense that they involve changes in the genetic material, but if they are severe enough to kill or sterilize the affected individual they are not inherited i.e. passed from parent to child. But it is quite possible for a chromosomal abnormality to be inherited, e.g. Down's Syndrome or Mongolism (Trisomy of chromosome No. 21).

Will it Happen Again?

A couple who have produced an abnormal baby naturally wish to know, "should we have another baby? Will it be normal?".

Accumulated knowledge about the mode of inheritance (autosomal dominant, autosomal recessive, sex-linked recessive), permits the genetic counsellor to estimate the risk to a subsequent child.

Counselling is relatively simple in autosomal dominant disorders, provided the diagnosis is unambiguous. If neither parent is affected, the affected child probably represents a *new* mutation, and parents can be assured there is little risk to future siblings. However, if the condition is known to skip a generation occasionally, or has a variable age of onset, the counselling must be more cautious.

In autosomal recessive conditions, birth of an affected child leads to the surmise that both parents are carriers. The risk that a second child would be affected is 1:4. Because of the recessive nature of the condition, the affected individual (heterozygote) cannot produce an affected child unless the other parent is a carrier, but all his offsprings will be carriers.

Counselling in X-linked disorders usually turns on whether the mother is a carrier. If she has two or more affected sons, or one affected son and an affected male relative (brother, father, maternal uncle) she must be considered a carrier. A single affected son, however, may represent either a hitherto occult mutation in the mother's ancestors or a new mutation. Sometimes, special tests of the mother can settle this point. When the mother's carrier status is known and diagnosis is unambiguous, counselling can usually be given. Hemophilia and

muscular dystrophy are two well known examples in this category.

Increasingly the doctor will be asked not merely, "should I have another child?" but, "should I have *this* child?" In some cases information obtained through *amniocentesis* can help provide an answer. Suspected chromosomal disorders have been detected through examination of fetal cells, and certain enzymatic defects also seem to be detectable, although some times more elaborate techniques are required. In the case of sex-linked diseases, determination of the sex of the embryo (which can be reliably done by cytologic techniques) will at least narrow the possibilities, even when the disease itself cannot be identified in utero. For instance a female carrying the haemophilia gene might well choose abortion of a male fetus, which has a 50 per cent chance of being diseased, while carrying to term a female fetus, who at worst would be a carrier.

Where termination of pregnancy is possible and legal, giving such advice is always a delicate business. It can cause family discord if the condition is such that it can be "blamed" on one or the other side of the family.

Prenatal Diagnosis of Genetic Disease

More than 1600 human diseases caused by defects in the content or the expression of the genetic information in DNA have been identified. Some of these diseases are very rare. Others like sickle cell anaemia and thalassaemia, and cystic fibrosis are relatively common and are responsible for much morbidity and mortality. Probably more than 25% of the hospitalisations of children are for illnesses with a major genetic component. Thanks to new techniques of biochemisty and cell biology, we are learning a great deal about the biochemical mechanisms that lead from a genetic defect to clinical disease. Cells from patients can now be grown and studied in tissue culture in artificial nutrient media; these cells often continue to express the abnormal function of the mutant gene.

Amniocentesis is now commonly performed between 12 and 16 weeks of gestation. Ultrasonography makes the procedure safe by the ability to locate the placenta. Amniocentesis yields a fluid, as well as cells suspended in the fluid. Biochemical tests are performed on the fluid immediately. The culturing and assay of amniotic cells require an additional three to four weeks.

It is fortunate for the geneticist that the lowly fibroblast has turned

out to have such a wide repertory of enzyme activities. It was not anticipated by many at least, that fibroblast cultures from skin biopsies would be almost as useful as liver tissue, for example, in studying diseases such as homocystinuria, when direct assay shows no significant amount of the relevant enzyme, cystathione synthetase, in skin. The development of prenatal diagnosis of inborn errors of metabolism depends also on this fortunate circumstance. If the fibroblasts of amniotic fluid did not have the same wide range of enzymatic capacities in culture, their deficiency in genetic diseases could not have been determined. The exceptions such as phenylketonuria (phenylalanine hydroxylase is normally not present in skin or amniotic fluid fibroblasts) serve to underscore the good fortune of geneticists in the study of cultured fibroblasts.

Recombinant DNA, Genetics and Medicine

Development of recombinant DNA technology has now made it possible to isolate DNA sequences or genes from mammalian cells and to replicate these genes in bacteria. For the clinician, they have provided the means for identification of mutations, the diagnosis of affected and carrier states for heritable diseases, the mapping of human genes on chromosomes, the isolation and alteration of genes, the transfer of genes from one organism to another, and the production of hormones, vaccines and other biological agents of pharmacological importance. The recombinant DNA technology opens up fantastic new vistas for medicine.

Discovery of restriction endonucleases has made it possible to fragment the huge DNA molecules that comprise the 46 human chromosomes into smaller fragments and consequently to isolate genes from these large molecules. These restriction enzymes, isolated from bacteria, cleave DNA only at specific DNA sequences. In this way, restriction endonucleases allow the reproducible fragmentation of DNA, analogous to the reproducible fragmentation of proteins by proteases such as trypsin. Thus a piece of human DNA cleaved by a particular enzyme, say ECo R1 which recognizes the sequence 5'GAATTC3', can bind to a piece of bacterial DNA cleaved with the same enzyme, and the two nicks in the resultant single molecule of DNA can be repaired by the enzyme DNA ligase to form an intact, new and hence *recombinant DNA molecule.*

Clinical Implications

Human genes can now be isolated and analyzed, and their RNA and protein derivatives can be produced in vitro and in vivo. The ability to

clone and sequence the human α and β globin genes for instance, made it possible to define multiple causes of the thalassemic syndromes.

Any fetal cell, including amniotic fluid cells, can be utilised to analyse alterations of a particular gene causing a particular disease. For instance, to detect the sickle cell gene, the DNA from the amniotic fluid cells is cleaved with a restriction endonuclease, and the resultant DNA fragments are separated by size using gel electrophoresis. The DNA is then transferred to a sheet of nitro-cellulose and hybridized with a radioactive copy of previously cloned human B globin. The radioactive β globin DNA binds only to the DNA fragments containing B globin sequences and this binding is detected by autoradiography.

The normal β globin gene has the nucleotide sequence CCT *GAG* GAG corresponding to the amino-acids proline-glutamic acid-glutamic acid at one specific region in the gene. In contrast the sickle beta globin gene has the sequence CCT *GTG* GAG corresponding to the amino-acids proline-valine-glutamic acid at the corresponding positions. One restriction endonuclease cleaves DNA at the sequence CCTGAGG but not at the CCTGTGG and therefore cleaves the normal but not the sickle gene. The cleaved normal DNA has a different electrophoretic mobility from that of uncleaved (sickle) DNA and the two can be easily distinguished. Of course, not all abnormal genes are associated conveniently with an alteration in a restriction endonuclease cleavage site. Nevertheless, the blot hybridization technique is likely to find increasing applicability in gene mapping and prenatal diagnosis. Digestion patterns generated by particular enzymes differ so often in the population that it is frequently possible to associate mutant gene with a nearby restriction enzyme site. Family studies then make it possible to associate specific restriction enzyme patterns with particular paternal and maternal chromosomes.

The same kind of analysis that is used to diagnose abnormal human genes can also be used to detect viral DNA genes in cells and tissues. For instance, from liver biopsy sample of patients with hepatoma or chronic active hepatitis, hepatitis viral DNA can be detected. The diagnosis of cytomegalovirus will be facilitated by similar sensitive hybridization assays using cloned DNA.

Therapeutic Implications

A major objective of recombinant DNA technology is to produce proteins, enzymes and hormones of human interest, in micro-organisms.

To replicate in bacteria, human DNA must be linked to specific DNA sequences that direct bacterial DNA replication. A technique that is basic to much of the progress in this field is *gene splicing.* In concept, it is simple but in practice it is complex. A favourite organism for recombinant DNA technology is a mutant of Escherichia Coli that is unable to synthesize the essential amino-acid tryptophane. There are circular forms of DNA (plasmids) that contain a gene for making tryptophane. A foreign gene can be spliced into these plasmids near the tryptophane gene in such a manner that the foreign gene and Tryptophane gene will be expressed simultaneously. Placed in a culture of the mutant E. Coli, some of these plasmids enter the bacterial cells, and by supplying the needed tryptophane, enable them to survive and multiply. Mechanisms within the E.Coli are such that a new plasmid may be replicated 20-40 times, within each bacterial cell. Since tryptophane is in great demand by the micro-organism, the gene for it, and simultaneously the foreign gene linked to it, are preferentially expressed. Therefore, the human gene product becomes quantitatively the major protein in the bacterial cell. Human insulin, growth hormone and interferon synthesized in bacteria have already been used in clinical trials, and the Hepatitis B antigen has been synthesized for use in vaccines.

Apart from bacteria, other living cells like yeasts or mammalian cells can also be employed in recombinant DNA technology and gene splicing. The choice depends upon the particular goal.

For instance, for the production of vaccines, yeast cells may be more suitable. They also have plasmids, like bacteria, which could be used for gene splicing. Unlike E.Coli, yeasts produce no endotoxin, and can secrete protein in the medium. Additionally, since they are eukaryotes, yeasts can synthesize glycoproteins (unlike E.Coli). Because of these attractive features yeast is being increasingly employed for recombinant DNA work, for example, for the production of human interferon for therapeutic uses. Truly, we are on the threshold of a new therapeutic revolution.

Chapter 9

NUTRITION, ANCIENT AND MODERN

Introduction

Mankind has always been interested in food. The practice of dietetics is an ancient, empirical and some times elegant art. It is only in the present century that it has also become a science, that tells us what nutrients we need, why we need them and from what foods they may be obtained.

Charaka says in praise of food: "The life of all living things is food and all the world seeks food. Complexion, clarity, good voice, long life, understanding, happiness, satisfaction, growth, strength and intelligence are all established in food."

"Food is the foremost among those that sustain life; water among these that are refreshing agents; wine among acopies; milk among vitalizers; flesh among roborants; meat juice among demulcents; salt among appetisers; acid juices of fruits among cordials; the flesh of the cock or hen among promoters of strength".

"Aharatattva" or dietetics forms an important part of Ayurveda. *Charaka Samhita* describes in great detail the digestibility, nutritive value and medicinal value of hundreds of different palatable substances of various classes. It points out that all such substances can gain in nutritive value or become harmful by combination with other items, by cooking or preparation, and according to quantity taken, palatability, appetite, bodily health, local climate, season and eating habits. A list of substances which are incompatible with each other, or unwholesome in particular seasons, is given.

"Wholesome" and "Unwholesome" Food

In *Charaka Samhita* one finds the following interesting dialogue:

"What is the factor that promotes the growth of man?"

"The use of a wholesome diet is the only factor that promotes the

healthy growth of man, and the factor that makes for disease is the indulgence in unwholesome diet''

''How shall we know unerringly the characteristics of both the wholesome and the unwholesome varieties of diet?''

''That class of foods which helps the harmonised body elements to retain their state of equilibrium and the discordant body elements to gain equilibrium, is the wholesome one, and the unwholesome one to be that which acts in the opposite manner. This definition of the wholesome and the unwholesome will be found to be infallible''.

''Food is all of one kind, eatability being the common feature. But it is of two kinds as regards its sources, one is inanimate and the other animate; it is also two-fold in respect of its effects, being either wholesome or unwholesome''.

Thanks to the tremendous advances in physiology and biochemistry, the twentieth century Science of Nutrition has been able to elaborate in great detail the ''wholesome'' and ''unwholesome'' aspects of diet, as we shall see in this chapter.

Energy Requirements

Charaka states: ''Even light, easily digested and nutritious food should not be taken in excess of bodily requirements, or after the appetite has been satisfied. Food difficult to digest should not be taken habitually. If ever used, the quantity should not exceed a fraction of a full meal''.

What constitutes *excess* over the *normal* body requirements as indicated by Charaka? How to assess normal body requirements of food? The science of Nutrition has been able to tackle these questions and provide useful answers, although some nutritionists think we still do not know what is *optimum nutrition.*

Antoine Lavoisier (1743 – 1793) proved that there existed a close similarity between breathing of air by the human body and the combustion of a substance in air. In both, the oxygen in the air was consumed, being replaced by carbon-dioxide. He further observed that a man at work consumes more oxygen than the one at rest. It thus became known that the food we eat is somehow transferred into energy and heat inside the body.

Animals including man get their energy from their food in a chemical form, in the form of carbohydrates, fats and proteins. The energy is liberated and utilised for the performance of mechanical work, for maintaining the metabolic activity of liver, kidneys, brain

and the other organs, for maintaining the body temperature and for promoting growth by synthesis of new chemical substances rich in energy.

The unit of energy is the joule (J) and is the energy expended when 1 kilogram (kg) is moved 1 metre (m) by a force of 1 newton (N). Physiologists and nutritionists are concerned with large amounts of energy and the convenient units are the kilo joule (KJ or 1000 joules) and the mega joule (MJ or million joules). Formerly energy was always expressed quantitatively in units of heat, the unit being the kilo calorie, defined as the amount of heat required to raise the temperature of a litre of water from 15°C to 16°C. Conversion of Calories to joules is made by multiplying by 4.186, or roughly by 4.2.

The total energy expenditure is quantitatively related to the oxygen consumption. The measurement of oxygen consumption in man has been made with many different types of apparatus. The Benedict Roth apparatus is very simple to use and gives a direct reading of the oxygen consumption without the necessity of gas analysis. For measurement of energy expenditure during everyday activities of living, and during industrial work, the Max Planck respirometer is extremely useful. Many thousands of measurements of energy expenditure of men and women undertaking a great variety of activities have been made.

When a subject is at complete rest and no physical work is being carried out, energy is required for the activity of the internal organs and to maintain body temperature as already mentioned. This energy is called the *basal metabolic rate,* of BMR; it is expressed in KJ/Kg of body weight. Animals so diverse as man, mouse, dog and horse have very different BMRs. But if expressed in KJ/M^2/hour (surface area of the body) the figures for each species are remarkably similar. A nomogram is available to predict surface area from measurements of height and weight.

There are wide variations in the energy requirements of individuals, even of those following the same occupation and apparently leading similar kinds of lives. But when food is freely available, a healthy individual instinctively assesses his own energy needs with remarkable precision. The energy requirements of individuals are dependent upon four variables viz. physical activity, body size and composition, age and climate. There are also extra needs for growth in childhood and adolescence, and for pregnancy and lactation.

Recommended Daily Allowance

One of the earliest and best known attempts to make recommendations regarding nutritional needs of populations was made under the auspices of the League of Nations. This report was published in 1936 and influenced the thinking of nutrition workers throughout the world.

The recommended dietary allowances for calories for Indians, made by the Indian Council of Medical Research are given in Table I, according to the type of work.

Sedentary work: This category includes clerks, teachers, journalists, doctors, lawyers, shop-keepers, architects, drivers and pilots.

TABLE I

Recommended Allowances for Calories per day (ICMR)

Man (55 kg)	
Sedentary work	2400
Moderate work	2800
Heavy work	3900
Woman (45 kg)	
Sedentary work	1900
Moderate work	2200
Heavy work	3000
Pregnancy (later half)	+ 300
Lactation	+ 500
Children	
Under 1 year (0 – 6 m)	120/kg.
(7 – 12 m)	100/kg.
1 – 3 years	1200
4 – 6 years	1500
7 – 9 years	1800
10 – 12 years	2100
Girls 13 – 15 years	2200
16 – 19 years	2200
Boys 13 – 15 years	2500
16 – 19 years	3000

Moderate work: This category includes light industry and assembly plants, railway workers, postmen, plumbers, bus conductors, farm workers and builders' labourers.

Heavy work: This category includes coal miners, steel workers, dock workers, foresters and army recruits.

A simple commonsense guide for the adequacy of a given Calorie allowance is to watch the weight over a period of weeks. Steady weight in an adult would indicate adequacy, loss of weight would indicate deficit, and gain in weight would indicate surplus of calories over needs. If one overeats to a very slight extent of 0.05 per cent, he will acquire a modest middle-age spread amounting to some 28 pounds of weight. The gain in weight, though usual, is not healthy.

Self-regulation of feeding

A good example of the "wisdom of the body" in self-regulation of food intake was provided in 1969 by Ashworth. He provided unlimited food for eight children who were markedly underweight. At first their intakes were very large, about 670 KJ (160 KCal/kg/-day). However, when they had reached the normal weight for their height, they began to refuse food and reduce their intakes to 485 KJ (116 KCal/kg/day) sufficient to meet the normal requirements of growing children.

Feeding is controlled by centres situated in the hypothalamus, which is that small area of the brain lying beneath the main bulk of the cerebrum. If in rats the two ventro-medial nuclei of the hypothalamus (VMH) are destroyed by stereotaxic techniques using fine needles, the animal begins to eat voraciously and becomes obese in a few weeks. This can be attributed to the loss of a *"Satiety Centre"*. On the other hand, if the two ventro-lateral hypothalamic nuclei (VLH) are destroyed, the animal refuses to eat, though otherwise normal; unless fed forcibly it will die of starvation; this can be attributed to the loss of a *"Feeding Centre"*. Several regulatory processes have been proposed as modulators of these hypothalamic centres. Meal-induced gastric distension, level of insulin, total adipose tissue mass, may all influence the activity of the hypothalamic centre. Additionally the hypothalamic centres are sensitive to catecholamines; and beta-adrenergic stimulation inhibits eating behaviour. This provides at least one rationale for the appetite-suppressing effects of amphetamines.

Ultimately the cerebral cortex controls eating behaviour and impulses from the feeding centre to the cerebral cortex are only one input.

Psychological, social and genetic factors also influence food intake.

Changing Energy Requirements

Until 200 years ago, upto the Industrial Revolution, human muscles, supplemented by those of oxen and horses, mules and donkeys, provided the power that made civilization possible. Muscles did the work of the field, thrashed and ground the corn, built the great temples and palaces, transported men and their armies, and spun and wove the fabrics for clothing and tapestries. In the modern industrial societies all this has changed. With a flick of a switch now one can harness great power. There is little need now to use muscles for anything but the lightest activity. Hard labour, walking, running and bicycling are becoming more and more unnecessary due to increasing mechanisation, motorisation and automation. Evidently, *homo sapiens,* having become *homo sedentericus,* is paying the price for the change. Degenerative diseases including heart failure in middle age are more common in sedentary persons than in active ones.

The importance of regular physical exercise has therefore become all the more crucial, in the maintenance of health today, than ever before. (See chapter 14: "Exercise in Health & Disease")

Modern Concept of "Proper Nutrition"

The body contains many thousands of species of organic molecules but requires for health the intake of only *23 organic compounds,* in addition to a *source of energy* and *water:* nine essential amino-acids, one essential fatty acid and 13 vitamins or accessory food factors. The vast majority of organic molecules in food, although metabolized or assimilated by the body, are non-essential in the sense that their deletion from the diet does not cause illness. The simplicity of nutritional requirements of the healthy subjects compared with the complexity of the chemical composition of the body, is the result of the remarkable capacity for endogenous biosynthesis (see the chapter on "The Chemistry of Life").

Of the limited number of *inorganic compounds* in food, the majority of their constituent elements, which are 15 in number, are considered to be nutritionally essential; these are calcium, phosphorus, iodine, iron, copper, cobalt, zinc, magnesium, potassium, sodium, chloride, chromium, manganese, molybdenum and selenium.

The symptoms and manifestations of nutritional deficiency, are now well recognized.

The requirement of an essential nutrient is the smallest quantity that maintains normal mass, chemical composition, morphology and physiological functions of the body and prevents any clinical or biochemical signs of corresponding deficiency state. In children, an additional criterion is a normal rate of growth.

Minerals

Ayurveda describes 9 kinds of salts and several kinds of minerals for use in human diet and therapeutics. These are described in Table II.

Mankind has used salt since antiquity. The first known salt mines have been found in the Austrian Tyrol and date from the late Bronze Age, about 1000 B.C. For at least 3000 years sodium chloride or common salt has played an amazingly important part in the lives of men. Wars have been fought over its sources and for centuries its trade was more important than that of any other material; this was because salt was the best preservative available.

A full account of the symptoms and signs of salt deficiency based on experimental depletion was given by Mc Cance in 1936, using himself and his pupil as subjects. The characteristic symptom is muscular cramp, which is well known to miners who work in hot pits, thereby losing a lot of salt through their sweat. Other symptoms are loss of appetite and vomiting, and mental apathy. Similar experimental depletion of many other elements has been studied in man, and animals.

The theory that man is descended from some remote marine ancestor is expressed in the Sanskrit description *"Amrutasya Putra"*, "son of the sea". It is consistent with the fact that his extra-cellular fluid has definite similarities in mineral composition to that of the sea as it was likely to have been many millions of years ago. Sea water contains measurable quantities of chloride, sodium, magnesium, calcium, sulphur, nitrogen, potassium, carbon, iodine and iron. It also contains traces of phosphorus, although the greater part of this element is taken up immediately by plankton, the floating organisms of the sea, and incorporated into their organic structure. All of these elements contribute to the nutrition of the human body. The knowledge about the importance of trace elements is very recent.

Many carcasses of small animals have been analysed chemically, but the results do not necessarily apply to man. A complete chemical analysis of the human cadaver is a formidable task which has been carried out on a number of occasions, but not sufficiently often to give the

TABLE II

Salts and Minerals in Ayurveda

Salts

1. Samudraka (Sea salt)
2. Baluka (Salt from saline sands)
3. Romaka, Pamsuja (Salt from saline soils or clay)
4. Maulaka (black salt)
5. Udbhida (Fossil salt)
6. Saindhava (Salt from ashes of marine plants)
7. Agrya lavana (Rock salt)
8. Sauvarchala (Salt obtained by boiling alkali with myrobalan)
9. Anupalavana (Salt obtained by evaporating well water)

Mixture of salts

Dve lavana (mixture of rock salt with alkaline salt)
Lavana traya (mixture of three salts)
Lavana chatvari (mixture of four salts)
Lavana panchaka (mixture of five salts)

Minerals

Ayas, Mandura, Loha (iron)
Tamra (Copper)
Gandhaka (Sulphur)
Trapu (Tin)
Mrt (Clay)
Istaka Churna (Brick powder)
Adrijatu, Shilajatu (exudate from ores)
Sarvaloha (tin, lead, iron, copper and silver)
Heman (Gold)

range of variations in people of different age and sex (*Widdowson et al* 1951).

Twentieth Century Science & Technology have given us a new tool for the study of trace elements, which is most sensitive and most accurate. As many as 70 elements can be measured in the range of 10^{-6} to 10^{-12} g, by the method of *neutron activation analysis.* The principles on which activation analysis is based are fundamental to the physical basis of nuclear medicine. In a typical analysis, the sample to be analysed is exposed to an intense beam of neutrons which interact with the nuclei of the atoms in the sample to produce radioactive and stable isotopes. Each radioactive isotope is uniquely characterized by its rate of decay and the type of radiations emitted; therefore positive identification and quantitative measurement of the radionuclide is possible. The amount of an element in a sample can be determined directly from the radioactive measurement because the induced radioactivity is directly proportional to the number of the atoms of the stable isotope in the original sample and to the neutron flux that interacts with the stable nuclei.

The role of trace elements in biology has been recently appreciated. Deficiency diseases can be caused by a lack of essential trace elements, and high dietary concentrations can be toxic.

It is worth knowing why the 15 elements considered to be essential for nutrition, are so important.

Calcium is the most abundant mineral in the body. It makes up about 1.5 to 2 per cent of body weight and 39 per cent of the total mineral content. In addition to the major function of calcium to build and maintain bones and teeth, the remaining 1 per cent of the body's calcium is found in the body fluids and soft tissues. Ionic calcium is essential for the activity of certain enzymes, notably ATPase in the release of energy for muscle contraction and for the activity of c AMP. In the blood clotting process, calcium must be present to initiate the changes needed for the formation of the clot, fibrin. Calcium affects the transport function of cell membranes, possibly acting as a membrane stabilizer. Calcium also influences transmission of ions across membranes of cell organelles, the release of neuro-transmitters at synaptic junctions, the synthesis, secretion and metabolic effects of protein hormones and the release or activation of intracellular and extracellular enzymes. There are minute amounts of calcium in the cytosol; it is found in mitochondria and endoplasmic reticulum as a phosphate salt.

Calcium is required in nerve transmission and regulation of heart beat. The proper balance of calcium, sodium, potassium and magnesium ions maintains muscle tone and controls irritability.

Phosphorus is one of the most essential elements, second to calcium in abundance, comprising 22 per cent of the total body mineral content. In addition to its structural role, phosphorus has numerous functions more than any other mineral element. Phosphorus is an essential component of nucleic acids; and phospholipids are key components in the structure of cell membranes. Glucose is phosphorylated as the first step in its utilization and at other steps. High energy phosphate compounds play a central role in many reactions, as does cyclic AMP. Phosphorus is part of some conjugated proteins, for example milk casein. Many of the B vitamins function as coenzymes only when in combination with the phosphate. The phosphate buffer system is important particularly in intracellular fluid, where its concentration is much higher than in extracellular fluid, and in the tubular fluids of the kidney.

Sulphur occurs principally as a constituent of the amino-acids cystine, cysteine and methionine. It is present in all proteins but is most prevalent in the keratin of the skin and hair (4 to 6 per cent sulphur) and in insulin (3.2 per cent sulphur). Glutathione, a tripeptide containing cysteine, is important in cellular reactions involving the sulphur amino-acids in protein. Sulphur exists in a reduced form (– SH) in cysteine and in an oxidised form (– S – S –) as the double molecule, in cystine. This is important in the specific configuration of some proteins and in the activity of some enzymes. Sulphur also occurs in carbohydrates such as heparin, and chondroitin sulphate in bone and cartilage. Two vitamins, thiamine and biotin, contain sulphur. The poisonous effects of many heavy metals (arsenic, mercury, lead) are due to their ability to combine with sulphydryl groups.

Magnesium is essential for the production and transfer of energy for protein synthesis, for contractility of muscle and excitability in nerves. It is an essential co-factor in numerous enzyme systems related to other functions. Magnesium and calcium, having similar functions, may antagonise each other. An excess amount of magnesium will inhibit bone calcification. In normal muscle contraction, calcium acts as a stimulator and magnesium as a relaxer. An excessive amount of calcium may induce signs typical of magnesium deficiency.

Iron plays a crucial role in the transport of oxygen from the lungs to the tissues, in the transport of CO_2 away from the tissues to the lungs, and in the process of cellular respiration. Haemoglobin, myoglobin and

the cytochromes are the iron-containing proteins and enzymes mediating oxygen transport. There is evidence from animal studies that in dietary iron deficiency the concentration of the respiratory cytochrome enzymes may drop before the haemoglobin level in the blood drops. Iron may play a role in the conversion of beta-carotine to Vitamin A, the synthesis of purines, the clearance of blood lipids and the detoxification of drugs in the liver. Lactoferritin in breast milk is an iron-containing protein effective against E.Coli of the gastro-intestinal tract of infants.

Fluorine is mainly important in relation to protection of tooth enamel against caries, but it seems to be an essential trace element in animal feeding experiments. The skeleton of the average man contains 2.6 gm. of fluorine. The fluoride content of food varies according to the content of the soil in which it is grown. In certain parts of India the water sometimes contains 10 – 45 ppm (parts per million parts). Over a period of years it produces excessive fluoride deposition in bones and consequent pressure effects on the nerves and the spinal cord. The disease is called fluorosis.

Zinc plays a role in a number of metabolic activities. There are 70 or more metallo-enzymes that require zinc to function. These include carbonic anhydrase, alkaline phosphatase, lactic dehydrogenase and carboxy peptidase. Zinc functions by maintaining spatial and configurational relationships necessary for enzyme action. In this role it helps to bind enzymes to substrates and may modify the molecular shape of enzymes by simultaneously combining with amino-acids at different places on the protein, thus affecting secondary, tertiary and quaternary protein structure. A number of zinc metallo-enzymes are involved in the regulation of cellular growth.

In addition to its function in enzymes, zinc participates in the metabolism of nucleic acids and the synthesis of proteins. Zinc may also have an important role in cell division since zinc deficiency causes adverse effects on the incorporation of labelled thymidine into the DNA of rats. Zinc is required for DNA synthesis, and the DNA-dependent RNA polymerase is a zince dependent enzyme; so is thymidine kinase. Zinc is essential for wound healing, for defence against infection especially of the skin surface.

Zinc deficiency causes ageusia, loss of hair, night blindness and a skin rash, often associated with the staphylococcal and yeast infection which respond only to zinc supplementation.

Sodium Chloride: Sodium, chloride and potassium are so intimately related in the body that it is most convenient to discuss them together. Sodium constitutes 2 per cent, potassium 5 per cent and chlorine 3 per cent of the total body mineral content. They are distributed throughout the body fluids and tissues, but sodium chloride is primarily extracellular while potassium is mainly an intra-cellular element. All three are involved in at least four important physiological functions of the body, namely water balance, osmotic equilibrium, acid-base balance and normal neuro-muscular irritability. Hormonal control of sodium, potassium and chloride is mediated through the adrenal cortical hormones. Adrenal cortical insufficiency, or certain conditions such as marked vomiting and diarrhoea, burns, prolonged diuretic therapy will result in "low salt syndrome".

Potassium, apart from playing an important role in the maintenance of water balance, osmotic equilibrium and acid base balance, is also important along with calcium in the regulation of neuro-muscular activity. Potassium level in the muscle is related to muscle mass; therefore if muscle is being formed, an adequate supply of potassium is essential. The same applies to glycogen storage. Very low serum levels (less than 2mEq/L) of potassium lead to sudden cardiac death, while very high serum levels (over 8mEq/L) can lead to death by cardiac asystole.

Iodine is unique among the essential mineral elements in that it is an essential component of specific thyroid hormones. The adult human body normally contains 20 – 50 mg. of iodine of which 8 mg. is concentrated in the thyroid. In Himalayan and other mountainous regions of India and the rest of the world, the deficiency of iodine leads to goitre; such gland contains less than 1 mg. of iodine. Addition of sodium iodide to the common salt sodium chloride (in a proportion of 1 part to 50,000 parts) has beneficial consequences. Sea-food (fish) is an excellent source of iodine.

Cobalt is unique in that it must be supplied entirely in its physiologically active form, cyanocobalamine or hydroxycobalamine (vitamin B12), which contains 4 per cent cobalt, and is the only cobalt-containing compound present in the body.

Chromium in the form of a low molecular weight organic complex, glucose tolerance factor (GTF), is required for normal glucose metabolism in several animal species including man. Deficiency of chromium leads to glucose intolerance and neuropathy in patients receiving long-term total parenteral nutrition, which is reversed by chromium supplementation.

Copper is a component of many enzymes including Cytochrome C oxidase and is important in cardiovascular and skeletal integrity, central nervous system structure and function, and erythropoietic function.

Selenium is an important constituent of glutathione peroxidase in erythrocytes; this enzyme protects against excessive accumulation of hydrogen peroxide. Deficiency of selenium has been associated with congestive cardiomyopathy and possibly muscle disease, in China.

Manganese activates a host of critical intracellular enzymes. Deficiency Syndrome in man has been described (weight loss, change in hair colour and slow growth of hair). Manganese toxicity in miners leads to a picture similar to Parkinson's Disease & Wilson's Disease.

Protein – Energy – Malnutrition

In a child deprived of food, growth stops almost immediately because of the high requirement of energy necessary to build protein. A child who has suffered undernourishment very early and for an appreciable length of time will never reach normal size for his age even though he is later fed well enough to restore a normal rate of growth. This is part of the reason for the small body size of many people in impoverished countries. The first year of life or the pre-weaning period is particularly critical for the brain is still growing and developing during this time. In experimental studies on rats and in analysis of the brains of children who had died of marasmus (emaciation due to energy deprivation), the underfed brain had a subnormal content of DNA. Starvation had interfered with cell division and left the animal or child with a permanent deficit in the number of cells in the brain. When the mother was underfed during pregnancy, in the rat experiments, malnutrition of the offspring after birth had an even more devastating effect on the brain.

Unfortunately, millions of Indian children are victims of protein energy malnutrition. "Kwashiorkor", was first described by Dr. Cecile Williams in 1933 in Ghana. The meaning of the word given to her by the Ga tribesmen was "the sickness the older child gets when the next baby is born". The typical clinical signs are apathy, loss of appetite, edema and changes in the skin and hair. On close examination of the blood and other tissues there is a marked drop in the concentration and activity of key enzymes, which are themselves proteins.

Nearly half the world's population is underfed or otherwise malnourished. The lives of the people in the developing world are

dominated by the scramble for food to stay alive. Such people are perpetually tired, weak and vulnerable to disease. Because their under-nourishment begins soon after birth, it produces permanently depressing and irremedial effects on the population as a whole.

Importance of Breast Milk

Ayurveda stresses the importance of breast milk for infant feeding. *Kashyap Samhita* (which deals with paediatrics) defines "pure breast milk as that with which the baby thrives well and both the mother and baby remain happy, healthy and free from any ailment. Breast milk promotes growth and development, and acts as a tonic for all tissues. It increases the body resistance to various diseases. It promotes healing of wounds".

"Love and affection for the baby are essential for the secretion of breast milk. Hence looking at, handling, carrying the baby or even remembering the baby promotes secretion of milk. Happy state of mind and adequate rest and sleep are important for increasing breast milk supply. The mother should take plenty of milk, meat, ghee and oil and plenty of fluids to help increase the quantity of milk".

"Absence of maternal instinct, or fear, anger, sorrow and grief suppress the secretion of breast milk. Starvation, fasting, or inadequate diet, exertion and fatigue suppress the breast milk".

"If the mother does not have enough breast milk or if she is sick or her milk is grossly vitiated, it is better to employ a "Dhatri" or wet-nurse as no other milk can compete with human milk. The wet-nurse should belong to a good family, should be healthy, well built and good complexioned; she should take regular well-balanced diet and should not be suffering from any disease. Her breasts should be well-developed and nipples well-formed and protruding". Vagbhata suggests that "it is better to employ two wet-nurses so that they can feed their own babies adequately. However, it is important not to have more wet-nurses as the mixture of milk with different qualities can upset the baby".

A wide variety of medicines have been prescribed in Ayurveda for "purification of breast milk".

Ayurveda also gives details of the qualities of cows' milk, also milk from goats, buffaloes, asses, horses, sheep, camel and elephants.

Supplementary feeds are recommended at the age of 6 months when the infant cuts its teeth. Even if the infant does not cut its teeth, the

supplementary feeds must be started by the age of 10 months.

The current enthusiasm in the western world about the breast feeding of babies is "rediscovering the wheel" so far as the Indian mothers are concerned.

Nutritional Needs for Lactation

The period of lactation is a time of even greater nutritional stress for the mother than that of pregnancy. It is estimated that 1000 food calories are required to produce 600 calories of human milk. The fact that many Indian mothers in low-income groups have been observed to lose weight while nursing a baby indicates clearly that their calorie and possibly their protein need is not adequately met. Mothers with deficient diets produce milk with low vitamin and mineral content. Table III compares the vitamin content of human milks from different countries.

TABLE III

Comparison of Vitamin Content of Milk

Country	*Vitamin A IU/100 ml*	*Riboflavin mg/100 ml*	*Vitamin C mg/100 ml*
India (Low socio-economic level)	70	17	2.6
Great Britain (Low nutritional intake)	153	26	3.2 to 4
USA (Superior nutrition)	180	47	4.4

The calcium and phosphorus in milk are supplied from the mother's diet or withdrawn from her bones. It is not surprising that women losing 300 mg. of calcium per day in milk and consuming low calcium diets for a succession of pregnancies suffer severe calcium deficiency. This has been most frequently observed in regions where there is lack of vitamin D. In overcrowded, congested areas in Bombay where Muslim women observe purdah and live indoors, there is no opportunity to absorb the ultraviolet rays of the sunlight to produce calciferol in the skin. Hence it is comparatively common to find osteomalacia associated with pregnancy and lactation.

Dr. Gopalan at the National Institute of Nutrition, Hyderabad, has pointed out that inspite of their inadequate diets poor Indian mothers are able to breast-feed their infants successfully over long periods. Many produce from 400 to 600 grams of milk daily for periods extending over a year. The concentrations of calcium and iron in their milk samples were comparable to the normal range, although the mothers had poor calcium intake and were anaemic. Through this adaptive mechanism nature protects the baby at the cost of the mother.

In India, the high maternal mortality rate is influenced by the prevalence of iron-deficiency anaemia. Fetal iron stores are influenced by the mother's iron nutrition, during pregnancy. The normal full-term infant born of a non-anaemic mother usually possesses adequate iron store so that little is needed for several months. This is important because breast milk does not contain much iron. The high incidence of anaemia in many groups of Indian infants under six months suggests low iron storage before birth, because the mother's diet was lacking in iron. Experiments with radioactive iron indicate that the transfer of iron from the mother to the baby is most pronounced in the last 10 weeks of pregnancy. This explains the wide prevalence of severe anaemia in the later months of pregnancy. The iron deficiency can be very effectively treated by the use of medicinal iron.

Recognition of the nutritional needs of pregnancy are indicated in the difference between the recommended daily allowance for the non-pregnant women. The ICMR recommendations (1968) are shown in the Table IV below:

TABLE IV

Condition	*Calories*	*Proteins grams*	*Calcium grams*	*Vit. A I.U.*	*Riboflavin mg.*	*Thiamine mg.*	*Niacin mg.*
Non-Pregnant (sedentary work)	1900	45	0.4-0.5	3000	1.0	1.0	13
Pregnant (last-half)	2200	55	1.0	3000	1.2	1.2	15
Lactating mother	2600	65	1.0	4600	1.4	1.4	18

Concept of "Harmful Foods"

In Ayurveda there are descriptions of combinations of foods which are to be avoided. Some examples:

"Fish should not be eaten in conjuction with milk; one is cold, the other is hot. Being thus incompatible they tend to vitiate the blood and tend to cause obstruction of the channels".

Modern science of nutrition does *not* validate this belief. It is difficult to differentiate facts from fancy because in all societies many superstitions and food fads have existed since time immemorial. Some examples:

"The flesh of domesticated wet, land or aquatic creatures should not be eaten in conjunction with honey, til, gur, milk, black gram, garden radish, lotus stalks or sprouted grains.

"It is on account of such mixed diet that one develops deafness, blindness, tremors, idiocy, indistinctness of speech, nasal articulation, or comes by one's death".

"Jatuka-Sakha and ripe tokoocha must not be eaten with honey or milk. Such practice brings about death or the loss of strength, complexion, radiance, virility and potency".

One wonders what could have been the basis for these statements. What is the modern counterpart of "harmful" foods?

There is a long list of foods containing pharmacological or toxic agents known to have an adverse effect on human health, for which scientific explanation is available.

A sample list is given in Table V. *(See next page.)*

A monograph prepared by the Food Protection Committee (1966) of the U.S. Food and Nutrition Board, and another by Liener (1969), contain much curious information, and both are very readable.

Nature of "harmful Foods"

Foods which contain all of the important nutrients needed by the body may yet not be safe to eat. This may be true for a variety of reasons.

TABLE V

Some Possible Pharmacological or Toxic Effects of Foods

Item	*Active agent*	*Effects*
Ackee fruit	L-amino-B methylene cyclopropane propionic acid	Hypoglycaemia—vomiting sickness
Almonds, Cassava	Cyanide	Interference with tissue respiration
Bananas	5-hydroxy tryptamine	CNS & peripheral nervous system effects
Brassica seeds vegetables	Thio-oxyazodiline Thiocyanate	Goitre
Cheese of some varieties	Tyramine Nitrosamines	Raised blood pressure Liver damage, Cancer
Cycad nuts	Methylazoxy methanol	Liver damage, Cancer
Fish of some varieties	Various, seasonal or confined to certain organs	Toxic CNS effects
Fungi of many kinds	various	CNS and liver toxicity
Green potatoes	Solanine, other sapotoxins	Gastrointestinal upset
Legumes	Haemagglutinins	Red cell and intestinal cell damage
Mussels	Due to consumption of dinoflagellate, Gonyaulax	Tingling, numbness, muscle weakness, respiratory paralysis
Mustard oil	Sanguinarine	Epidemic dropsy
Quail	due to consumption of hemlock	Hemlock poisoning
Rhubarb	Oxalate	Oxaluria
Soya beans	estrogens	Similar to female sex hormone
Some other beans	Vicine B-aminopropionitrile	Favism-Haemolysis Interference with collagen formation

Wholesome foods are sometimes *adulterated* by the addition of harmful substances and thus become unsafe. Substances used to destroy insects or pests may be present in food and may make it harmful. The food may contain harmful micro-organisms or their products. Food-borne infection is a reflection of poor hygiene. In India, salmonellosis including typhoid fever, amoebic and bacillary dysentery, abdominal tuberculosis and brucellosis are common problems spread by contaminated food and water. Animal parasites (Trichinosis, flukes, tapeworms, roundworms) are also conveyed by foods.

Some of the most potent toxins are found in fungi which may contain otherwise healthy foods. *Ergot* is a fungus infesting rye, and outbreaks of ergotism have occurred in times of food scarcity. *Aflatoxins* can contaminate many human foods like groundnuts. Aflatoxins damage the liver and lead to cancer in many animals e.g. monkeys. Their role in human cirrhosis and liver cancer is conjectured. Some discussion of dietary carcinogens would be appropriate at this point.

Dietary Carcinogens

Dr. Bruce Ames has reviewed in 1983 (*Science,* issue of 23rd September) the increasing body of evidence that large numbers of potent carcinogens arise from natural processes. Mutagens are present in substantial quantities in fruits and vegetables. Carcinogens are found in cooking as a result of reactions involving proteins or fats. A variety of hydroperoxides, enals, epioxides and other reactive chemicals are produced by rancid fats, and rancid meat. Dietary practices may be an important determinant of current cancer risks.

Carcinogens and mutagens are present in mould-contaminated foods such as corn, nuts, peanut butter, bread, cheese and fruit. Some of these contaminants, such as aflatoxin are among the most potent known carcinogens and mutagens. Nitrosamines and nitroso compounds are suspect as causative agents of stomach and esophageal cancer in humans. In the digestive system these nitrogen compounds are formed from nitrate and nitrite. Beets, celery, lettuce, spinach, radishes and rhubarb all contain about 200 milligrams of nitrate per 100 grams portion.

Rancid fats are possible causative agents of colon and breast cancer in humans. However, there are no direct estimates of the amounts of oxidized fats ingested by humans, and the unpalatable nature of rancid fats precludes their ingestion in significant quantities. Burnt and browned materials formed by heating proteins during cooking are highly mutagenic. Chemicals isolated from such products have been

found to be carcinogenic when fed to rodents. In addition, the browning reaction products from caramelization of sugars or the reaction of amino-acids and sugars during cooking contain a large variety of DNA-damaging agents.

Epidemiologists have noted marked differences in cancer rates between population groups. The general indication is that an increase in consumption of fibre-rich cereals, vegetables and fruits, and decrease in consumption of fat-rich products and excessive alcohol, would be prudent.

Fortunately we have in our diet many defence mechanisms to protect ourselves against mutagens and carcinogens. For instance tocopherol (Vitamin E) has protective effects against radiation-induced DNA damage and mutation, and dimethyl hydrazine induced carcinogenesis. *Beta carotine* is another antioxidant in the diet that could be important in protecting body fat and lipid membranes against oxidation. Carotinoids are free-radical traps and remarkably efficient quenchers of singlet oxygen (a very reactive form of oxygen which is mutagenic). However, a recent large scale case control study produced no evidence "relating intake or serum levels of anti-oxidant vitamins to a reduced cancer risk". A low-fat high-fibre diet not only decreases intake of fat soluble synthetic carcinogenic contaminants but also reduces the risk of cardiovascular disease and of diverticulitis.

Mustard Oil

In Bengal and Bihar mustard oil is the chief cooking fat. In many episodes of epidemic dropsy, the clues were analysed in the best detective manner by Lal and Roy and other workers, who showed that mustard oil was responsible for this disease. The toxin was not present in the oil from the mustard seeds themselves, but in oil from seeds of a poppy weed (argemone mexicana) which commonly grows in the mustard crops. The Argemone seeds contain an alkaloid *sanguinarine* which is toxic. Sanguinarine inhibits the oxidation of pyruvic acid, and as in wet beriberi, pyruvic acid may accumulate in the blood of patients suffering from epidemic dropsy. The anaemia which is common in these patients has the features of a pyridoxine responsive anaemia (Lele and Krishnaswamy, 1979).

Lathyrism

Hippocrates had noted that "At Ainos those men and women who continually fed on pulses, were attacked by a weakness of the legs

which remained permanent". As we recognize today, the description fits the condition of lathyrism which results from excessive consumption of *Lathyrus Sativus.* There is no parallel description in Ayurveda although the condition has been seen in some parts of India. An excellent account of the ravages of this ancient disease can be found in "Rambles and Recollections of an Indian Official" published in 1844 by a British soldier, General Sleeman. "During three successive years 1829-1831 the wheat crop was destroyed by severe hailstorm, lack of rain and blight. During that period the "teori" or "Kesari", a kind of wild vetch, which though not sown itself but is left to grow carelessly among the wheat and other grain, and given in the green and dry state to cattle, remained uninjured and thrived with great luxuriance. The villagers ate this, and in 1833 the sad effects began to manifest themselves. The younger population of this and surrounding villages, from the age 30 downwards, began to be deprived of the use of their limbs below the waist, in all cases sudden, but in some cases more severe than in others. About half the youth of both sexes became affected during 1833 and 1834 and many of them lost the use of their lower limbs entirely".

In some parts of India 4 per cent of the rural population even today is affected by lathyrism. Kesari dal has been deliberately sown along with wheat by farmers particularly in Madhya Pradesh, as a drought-resistant crop. If the rains are good, the wheat outgrows the lathyrus, of which little is harvested. If the rain fails and there is a poor crop of wheat, a useful harvest of lathyrus may be reaped and consumed for subsistence. A poor monsoon is generally followed by an epidemic of lathyrism. All individuals who obtain more than a quarter of their caloric intake from Lathyrus sativus are liable to get lathyrism.

A neurotoxin has been isolated from the seeds of Lathyrus sativus, known as BOAA (B-N-Oxalyl-amino-L-alanine). On analysis at the National Institute of Nutrition in Hyderabad, this substance has been found in samples of seeds in amounts upto 2 gm per 100 gm. The relation between intake of BOAA and the clinical features of lathyrism has not been worked out. Other neurotoxins have been isolated from seeds of the common Vetch (vicia sativa) which frequently grows as a weed in lathyrus crops.

Concept of Lethal Synthesis

Peters in 1963 coined the term "lethal synthesis" when he discovered that the *fluoracetate* of a plant that poisons cattle in the Transvaal region

of South Africa, makes use of the enzymatic machinery of the body to convert itself by synthesis into a very toxic *fluorocitric acid.* According to Peters a similar mechanism might be operating in lathyrism. "The example of lathyrism is so striking that it may prove to be a key problem whose solution may lead to other things."

Concept of Deficiency Disorders

Five major diseases, scurvy, beri-beri, keratomalacia, pellagra and rickets arise as a result of *deficiency* of certain specific essential chemical factors. In the writings of Hippocrates or in Ayurveda one does not find the clear concept of a specific deficiency disorder. Undoubtedly there was a lot of *intuitive wisdom in folklore* regarding the causation and prevention of these disorders, but it took mankind a long, long time to understand the basis of this intuitive wisdom. The story of scurvy is of great educational interest.

Scurvy was not clearly recognized by the Greek, Roman or mediaeval physicians. There is no word for it in Ayurveda although one might conjecture that some haemorrhagic manifestations described were due to scurvy. In the 15th century enterprising Europeans undertook long sea voyages. In 1497 Vasco de Gama sailed round the cape of Good Hope to reach Calicut on the Malabar Coast in South India. Scurvy broke out among his crew, killing 100 out of his 160 men. For the next three hundred years scurvy was a major factor determining the success or failure of all sea voyages, undertaken for trade, exploration or war. As early as 1535 the French explorer Jaques Cartier, whose crew was severely affected by scurvy in Newfoundland had noted that the local Canadian Indians knew that the juice of the leaves of a certain tree had remarkable anti-scorbutic properties. Similar value of a decoction of spruce or pine needles was well known to the Swedes at least as early as the 16th century.

The first controlled therapeutic trial ever undertaken was in relation to scurvy. James Lind, a Scottish Naval Surgeon in 1747 showed "the most sudden and visible good effects from the use of oranges and lemons in two scorbutic sailors who received them, while there was no change whatsoever in ten other scorbutic sailors who had identical clinical condition but did not receive them." Lind published in 1753, "A Treatise of the Scurvy". This information was successfully utilised by Captain James Cook during his long voyage round the world from 1772 to 1775. He took great care to replenish his supplies of fruits and vegetables whenever he touched land, with the result that there was

not a single case of scurvy in his crew. The effect of Lind's study on state policy was delayed by some forty years. It was not until 1795 that the British Royal Navy enforced the practice of supplying oranges and lemons to the crew. The disease, however, continued to linger for a further 50 years in the merchant navies of the world. In South Africa from 1898 onwards, serious outbreaks of scurvy occurred in people working in the gold mines, and by 1902 it was stated that the number of cases of Scurvy exceeded that of accidents. Although a recommendation for a supply of fresh vegetables and lime juice for the miners was made by a knowledgeable doctor, it took the Govenment there another 22 years to issue a minimum ration scale for miners, which not only abolished scurvy but led to a marked improvement in their health and efficiency.

Unfortunately good health lessons are often soon forgotten. In 1912, Captain Scott, a naval officer, ignoring the experience of the Royal Navy in the eighteenth century, planned an expedition to the South Pole without a single source of ascorbic acid in his food rations. The story of that expedition is now tragic history.

In 1907 Holst and Frolich discovered that guinea-pigs, like man and monkeys, are susceptible to scurvy. Thereafter the search for the active principle was directed towards isolating from citrus fruit juices the pure chemical substance that would cure scorbutic guinea-pigs. In 1932 Glen King isolated the vitamin from lemon juice and identified it with ascorbic acid which the biochemist Szent-Gyorgyi had isolated from adrenal glands, oranges and cabbages in 1928. Szent-Gyorgyi was primarily interested in the nature of substances with reducing properties in biological materials; he had not recognized the properties of ascorbic acid as a vitamin. Ascorbic acid is a simple sugar, and a most active reducing agent known to occur naturally in living tissues. Its chemical structure was elucidated by Haworth and Hirst in Birmingham, England and its synthesis accomplished in 1933.

In experimental ascorbic acid deficiency in guinea-pigs Wolbach of Harvard studied its effects on the microscopic structure of tissues. Ascorbic acid is necessary for the proper formation of the intercellular ground substance or matrix that binds together the cells in such tissues as capillaries, bone, teeth and connective tissue. In connective tissue fibroblasts synthesize the protein collagen which then forms extracellular fibrils, strands and bundles. Ascorbic acid is in some way necessary for the formation of hydroxy-proline, an amino-acid which forms about 13 per cent of the collagen molecule. In scorbutic guinea pigs the collagen gradually disappears and the supporting structure of the connective tissue collapses. Lack of intercellular cement substance

in the walls of the capillaries leads to their rupture and the production of petechial haemorrhages (bleeding spots).

Although the guinea pig enabled ascorbic acid to be discovered, it could not provide the information on human needs for the vitamin. The first man to attempt to induce Scurvy in himself was an Edinburgh-trained physician William Stark, who died in the attempt in 1770. This dangerous experiment was not repeated until 1940 when a yound American Surgeon John Grandon fed himself on a diet devoid of ascorbic acid. In a later experiment, use of radio-isotopes helped to establish that the size of the ascorbic acid pool in a well-fed man is about 1.5g of which about 45 mg is utilised daily. Clinical signs of scurvy appear usually after 30 to 70 days when the pool is reduced to below 300 mg and the rate of utilisation below 9 mg/day.

The Story of Beri-beri

Beri-beri was a common condition in many parts of the world. Towards the end of the 19th century several investigators were looking for the causative factor or factors. The impact of the newly emerging science of bacteriology was so great that every one was thinking in terms of causative germs; in fact 17 different organisms were confidently claimed to be the cause by various investigators!

Takaki, a Japanese naval doctor in the 1880's studied the conditions in which the disease occurred in the Japanese navy, and after detailed investigations of its incidence in relation to many environmental factors, he came to the conclusion that it was not an infection but a *dietary deficiency* which caused the disease. The proportion of polished rice in the Japanese diet was excessive, so Takaki thought that beri-beri resulted when the ratio of protein to carbohydrates was too low. Takaki tested his dietary hypothesis by sending a crew on a voyage with an improved diet, wherein a part of the rice ration was replaced by wheat bread and the allowance of milk and vegetables was increased. While experience on a naval training ship had earlier shown 169 cases of beri-beri out of 300 crewmen on a voyage lasting nine months, on the voyage this time only 14 cases of beri-beri occurred, all in individuals who had refused to take the condensed milk and meat ration. Takaki, later as Surgeon General enforced the improved diet in the navy with the virtual disappearance of beri-beri within a year—though for reasons which were entirely different from what Takaki imagined.

In 1890 the Dutch physician Eijkman, stationed in a military

hospital in Java, observed a disease in chicken and pigeons resembling human beri-beri. He fed some domestic fowls on the food provided for his patients suffering from beri-beri. He noticed that the birds developed weakness of the legs and head retraction. A new head cook at the Hospital discontinued this supply of superior "military rice" (highly polished rice) so that thereafter the birds had to be fed on "inferior" whole grain "civilian rice". The result was that the fowls recovered! Eijkman wrote:" A chance circumstance threw suspicion on the fowls' feed. The onset and cessation of the epidemic in the fowls, which lasted six months, coincided respectively with the introduction of refuse of cooked polished rice, and its subsequent replacement with raw whole rice".

Next came the experiment in which Eijkman proved that there was something existing in very small amounts in the germ and pericarp of rice, that was water-soluble and that protected fowls from a disease resembling human beri beri. Eijkman deservedly won the Nobel Prize many years later for his discovery which showed how beri-beri could be prevented and cured.

No less instructive in this story is the nature of the medical profession's reaction to Eijkman's studies, they were doubted and questioned for a decade. Manson, in his presidential address to the Epidemiological Society in London in 1901 entitled "the Etiology of Beri-beri", was not impressed by Eijkman's theory. According to Manson, the disease was purely an intoxication produced by a toxin elaborated by a germ. In Osler's "Principles and Practice of Medicine" of 1909 (7th Edition), the germ and food theories received equal notice, and the latter offered no hint that something might be *deficient* in a polished rice diet. In the same year Fraser and Stanton in Kuala Lumpur finally showed that human beri-beri responded in the same way as that of Eijkman's birds.

In 1911 Funk prepared an extract of rice pericarp which was therapeutically active in beri-beri.

Proof of Accessory Food Factors

Between 1906 and 1912, Frederick Hopkins in Cambridge, England carried out experiments which showed that young rats fed on a diet of milk protein casein, starch sugar, lard and inorganic salts failed to grow and finally died. The addition to the diet of only 3 ml of milk daily, supplying not more than 4 per cent of the total energy enabled the rats to thrive. He thus demonstrated the existence of an "accessory

food factor'' in milk. In 1913 two groups of American workers extracted this growth factor with ether, thus showing that it was fat-soluble. In the same year E. V. McCollum in U.S.A. showed by studies with rats that milk contained two growth-promoting factors: the one in butter he called ''fat-soluble A'', and the one in the fat-free portion was termed ''water-soluble B''. It was realised that there were several accessory factors, and as they were discovered they were called Vitamin A, B, C, D etc. The word ''vitamine'' was suggested by Funk in 1912 because he believed that all the accessory factors were vital amines. We know now that only a few of the vitamins are amines, but the name has stuck, albeit without the last ''e''. In the last 50 years most of the vitamins have been isolated, synthesised and given chemical terminology. For instance Vitamin A is *retinol,* Vitamin B1 is *thiamine,* and B2 *Riboflavin,* B6 *pyridoxine,* B12 *cyanocobalamin* and so on. It has also become possible to define in biochemical terms their exact role as co-factors in certain essential chemical reactions in the body. To learn exactly how this knowledge came about, we will go back to the story of beri-beri where we left it.

Concept of Biochemical Lesion

Thiamine (anti-beri-beri vitamin) was the first vitamin whose precise activity in the body was stated in biochemical terms. This was achieved at Oxford between 1928 and 1935. Peters (1963) has written a historical account of the work of his school, which illuminates the process of scientific discovery and development of new concepts. In brief, it was first demonstrated that lactic acid accumulates in the brains of pigeons in whom thiamine deficiency is experimentally induced, causing head retraction and opisthotonus. It was then found that minced brain tissue from such pigeons took up less oxygen than brain tissue from normal pigeons in the presence of added glucose or lactic acid, *in vitro* (in a test tube). This failure of oxidation could be corrected by adding thiamine in catalytic amounts to the brain tissue. It was thus established for the first time that a vitamin could be an essential part of an enzyme system. It was found that pyruvic acid also accumulated in the brain and blood of such pigeons and it disappeared on the administration of thiamine. It is now known that the pyrophosphate of thiamine is the coenzyme of carboxylase, the enzyme concerned with the decarboxylation and oxidation of pyruvic acid. It was a lucky circumstance that this work developed with thiamine and the pigeon's brain, as this vitamin and this tissue show the *biochemical lesion* better than any other yet found.

The clinical and pathological features of Wernicke's encephalopathy were described in 1881. It was usually encountered in chronic alcoholics and occasionally in excessive vomiting of pregnancy, and in terminal cachectic states. In 1934 it was observed that rats made deficient in thiamine developed focal vascular lesions in the brain stem. In 1938 it was observed that the characteristic lesions in the brain in Wernicke's encephalopathy were experimentally produced in thiamine-deficient pigeons. Subsequent studies confirmed the value of thiamine in this disorder. After the grim experience of prisoners of war in the Far East after the 1939 – 1945 world war, Wernicke's encephalopathy came to be regarded as cerebral beri-beri.

Today a specific test for thiamine deficiency is the measurement of the transketolase activity in the red blood cells with and without the addition of thiamine pyrophosphate (TPP). If TPP increases activity by more than 25 per cent, this indicates thiamine deficiency.

It is unfortunate that beri-beri still exists in many rice-eating communities. Infant beri-beri results from a thiamine-deficient milk from a deficient mother; it is responsible for a large proportion of infant death in the Phillipines, Burma, Vietnam and probably also in other rice-eating areas.

The Story of Pellagra

Pellagra was not known to classical and mediaeval physicians. There is no description in Ayurveda which suggests this condition. In India pellagra occurs sporadically in those parts where maize is a staple cereal. For instance, Shah and Singh in 1967 reported 128 cases, all maize eaters, admitted to the Udaipur Hospital in one year. Pellagra also occurs in the Jowar eaters in Andhra Pradesh, where it accounts for 1 per cent of general admissions and 10 per cent of mental hospital admissions in certain seasons.

The history of the search for the cause of pellagra illustrates very well how the growth of knowledge can bring together apparently contradictory theories and shows in the end that each has a substance of truth.

The maize theory was the obvious one because pellagra occurred in maize eaters; it was attributed to some hypothetical toxin in the maize, perhaps produced by bacterial fermentation during storage.

The protein deficiency theory was based on the observation that the diet of pellagrins was very poor in proteins.

Goldberger in U.S.A. between 1913 and 1928 made a systematic study of pellagra and its causation by a combination of the epidemiological and experimental approach. He demonstrated that pellagra is a deficiency disease and that the pellagra-preventing factor was water-soluble and heat-stable, and occurred in the same food stuffs as thiamine; but he died before the identification of nicotinic acid. Maize actually contains more nicotinic acid than oats, rye, white wheat bread and rice. The explanation is that most of the nicotinic acid in maize is present in a bound form, unavailable to the consumer. Also, the protein of maize is deficient in tryptophane, from which the body is able to make nicotinic acid.

Rickets

The discovery of the cause and cure of rickets is one of the great triumphs of biochemical medicine. Most people recognise rickets as a deficiency disease resulting from a lack of Vitamin D. Few people will know that rickets was the earliest air pollution disease. In England when soft coal was used in industry, near about 1650, rickets was first described in children belonging to poor people living in narrow, sunless alleys of factory towns and big city slums. This, as we know now, was because of a deficiency of solar ultra-violet radiation, which is necessary for the synthesis of Calciferol, the calcifying hormone released into the blood stream by the skin. Without calciferol not enough calcium is laid down in growing bones and the crippling deformities of rickets are the consequence. Either adequate sunlight or the ingestion of minute amounts of calciferol or one of its analogues therefore prevents and cures rickets.

Solar radiation may be blocked by many means among them being the industrial smog in London. The long dark winter of many north European countries forced prolonged confinement of infants indoors during winter. In 1906, it was noticed in Germany that all children who were born in the fall and died in the spring had rickets; those who were born in the spring and died in the fall were free of the disease. In 1909, G. Schmorl documented this marked seasonal variation in the frequency of rickets with a series of 386 post-mortem examinations carried out on children under four years of age.

In 1908, Theobald Palm, an English medical missionary who went to Japan, was struck with the absence of rickets among Japanese as

compared to its lamentable frequency among the poor European children. He wrote to other medical missionaries round the world. From the data it was deduced that rickets was caused by the absence of sunlight. "It is in the narrow alleys, the haunts and playgrounds of the children of the poor, that this exclusion of sunlight is at its worst, and it is there that the victims of rickets are to be found in abundance". The systematic use of sun baths was a logical preventive and therapeutic measure.

The first successful attempt to induce rickets experimentally in animals was made in 1908 at the University of Glasgow by Leonard Findlay. Puppies confined indoors in cages developed rickets; unconfined animals did not become rachitic.

Harry S. Hutchinson conducted a most clear-cut investigation in Bombay in the beginning of this century. He found no rickets at all among poor Hindus who subsisted on a pitifully inadequate diet but who worked outdoors all day, "and while at work left their young infants at some nearby point in the open air". In contrast he found that rickets was exceedingly common among well-fed Muslims and upper-class Hindus, whose women usually married at the age of 12 and entered "purdah" where the ensuing infants usually remained with their mother for the first six months of life in a semi-dark room in the interior of the house. Hutchinson concluded that "the most important etiological factor in the production of rickets is the lack of sunlight, fresh air and exercise". He proved the point by taking out 10 children of purdah-induced rickets out into the open air, "showing that removal of the cause removes the effect. All other factors remained constant and no medicine was given".

In 1919, a Berlin Paediatrician, Kurl-Huldschinsky tried the light from a mercury-vapour quartz lamp which includes the ultra-violet wave-lengths, on four cases of advanced rickets in children. He obtained complete cures within two months. In addition to providing a truly effective method of curing rickets, he proceeded to show that an endocrine hormone must be involved. He irradiated one arm of a rachitic child with ultra-violet rays. Then he showed, with X-ray pictures, that calcium salts were deposited not only in the irradiated arm but in the other arm as well. This proved that on irradiation the skin released into the blood stream a chemical that had the needed power to induce healing at a distance—in other words, a hormone.

In June 1924, Alfred Hess in New York found that ultra-violet irradiation rendered linseed and cotton seed capable of curing rickets.

Hess proceeded to show that a crude cholesterol and plant sterols, as well as the skin, acquired the property of curing rickets when irradiated by ultra-violet rays. In 1927 Otto Rosenheim and Thomas Webster showed that the plant sterol ergosterol (derived from ergot, a fungus) became enormously anti-rachitic when irradiated with ultra-violet light. A description of the nature of the skin hormone naturally released by irradiated skin was finally provided in 1936 by Adolf Windaus at the University of Gottingen. He demonstrated that 7-dehydro cholesterol is the natural pre-hormone that is found in the skin and showed how it became calciferol on ultra-violet irradiation.

Modern studies support the long-suspected fact that fish, unlike birds and mammals, are able to synthesize calciferol enzymatically without ultraviolet light. Shielded by water, fish receive essentially no ultra-violet (290 – 320 millimicron) radiation, and yet the blue fin tuna fish has upto a milligram of calciferol per gram of liver oil, enough to provide a daily protective dose of calciferol for 100 children. In the north of Europe fish has always been a staple diet, and so the normal diet tended to protect children against rickets. Slowly, over the years, the people of Scandinavia and Baltic regions became aware of the specific therapeutic value of cod liver oil which contains enough calciferol to protect against rickets if consumed in amounts equal to 4 grams of oil per day; and oil or fat containing calciferol preserves its efficay for a long time. In a controlled trial in Negro children in New York City, Hess in 1917 proved the prophylactic value of routine administration of cod liver oil. Mellanby in London in 1919 suggested that the efficacy of cod liver oil was "most probably due to vitamin A deficiency", which was obviously wrong. Mc Collum, the American nutritionist in 1922, went on to establish the difference between the active anti-rachitic factor in cod liver oil and vitamin A by showing that after having been aerated and heated cod liver oil could still cure rickets but had lost the ability to cure Xerophthalmia, which is due to lack of vitamin A. On this basis he called the cod liver oil factor "Vitamin D". Final recognition of the uniqueness of fish liver oils came from the finding that animal fats such as butter and lard have essentially no calciferol, particularly in winter; no non-fish diet of any kind could protect against rickets in a sunless environment. It was quite clear that cod liver oil was a medicine, and not a food. No specific medicine such as cod liver oil can be called a dietary vitamin unless it is present in normal foods in significant amounts. Orally administered thyroxine cannot be regarded as "Vitamin T" even though

patients with thyroid deficiency are cured by thyroid extract. Both endocrine secretions (thyroxine and calciferol) require external factors, incidentally, iodine in the case of Thyroxine and ultra-violet rays in case of calciferol.

It should therefore be considered that Calciferol is a hormone rather than a "Vitamin D"—it is a steroid hormone whose production rate is under physiological control rather than being left to the vagaries of diet. The recognition of calciferol as an ultra-violet-dependent hormone gives fresh meaning to a number of seemingly unrelated physiological and cultural adaptations. Tropical man probably avoids the danger of too much calciferol production by virtue of his dark skin; the melanin granules in the outer layer protect the lower layers of the skin. European man, on the other hand, needed to use all the scanty ultra-violet light available and consequently was gradually selected for an unpigmented skin.

It is paradoxical that in our land with plenty of sunshine, where the sun is worshipped as God Suryanarayana, rickets and osteomalacia should occur due to inadequate exposure to sunlight. The capacity of the skin to synthesize Vitamin D on exposure to sunlight is not affected by undernutrition and there is significant increase in serum 25HCC after as short an exposure to sunlight as 6.5 minutes.

Science and Technology for the Conquest of Hunger

Starvation and hunger have haunted mankind throughout recorded history. It was Malthus, more than any other single author who first put the omnipresence of hunger in a universal perspective. He argued that unless man regulated his rate of population growth, his numbers would soon exhaust the available food supplies and therefore perish.

Unfortunately, apart from that due to famines and floods, hunger is often man-made. Mahatma Gandhi, himself a strict vegetarian and an apostle of non-violence, said during the devastating Bengal famine in 1943, that with the vast availability of fish and sea-foods there was no reason why people should starve to death.

Modern Science and technology have shown spectacular ways for better food production as well as better food conservation and preservation. Chemical fertilisers, insecticides and pesticides, plant growth regulators, soil conditioners, all require capital investment but they would pay for themselves many times over in higher yields. Modern genetics has created high-yield disease-resistant varieties of seeds that

can increase food production several-fold. Irrigation of land and mechanisation of farming have contributed to the green revolution. Scientific animal husbandry can provide greater yield of milk and poultry products. Scientific storage of food at the right temperature and humidity with protection from rodents and insects, protective packing with polyethylene and other synthetic wrappings permit better food preservation.

Artificial enrichment of food with vitamins and minerals is another modern development that can help millions of needy people tremendously. Iodized salt can dramatically reduce the incidence of endemic goitre. Enrichment of wheat flour with thiamine, riboflavin and niacin, and that of rice with thiamine plus iron and calcium, will produce significant improvement in the health of most of ill-fed populations. The addition of *lysine* to wheat flour or bread can raise the proportion of the wheat's usable protein from about a half to two-thirds; and the amino-acid *threonine* could make grain protein almost as fully usable as the protein of meat and milk. The main problem so far is the cost of synthesis of amino-acids. As more of them are synthesised and the price is brought down, these products of laboratory chemistry will make it possible to turn grain into "meat" for the vast segment of world population which is vegetarian either by choice or by economic necessity.

When a properly processed oil seed meal (made from cakes that are left when the oil is pressed out of the seed) is mixed with a food grain in the ratio of 1:2 the combination contains about 25 per cent protein of meat-like high quality. With the addition of a small amount of yeast and vitamin A it will make a highly nutritious food.

In 1975, when the world population touched nearly 4 billion, the global food production was estimated at 3.3 billion tons. This target was achieved nearly 12,000 years after agriculture came into existence on planet earth. With the world population threatening to reach about 8 billions in the next 40 years, what is going to be mankind's response? The synthetic chemists do not share the pessimism of Malthus, since they visualise the prospects of manufacturing completely synthetic foods at a low enough cost, to end all food worries. After all, the essential nutrients man requires are basically chemicals whose formulae are well known. Modern technology could make micro-organisms do the food production for us when the resources of land and sea are exhausted.

Chapter 10

FEVER, SEPSIS AND MICROBIOLOGY

Introduction

The recognition of fever as a sign of disease goes back to ancient times. The Hippocratic corpus contains many precise descriptions of the temperature course in various types of fever. The *Charaka Samhita* and *Sushruta Samhita* describe different clinical types of fever, based on periodicity, like *"Santat jwar"* (continuous fever); *"Tritiyak"* (alternate day or tertian); *"Chathurthak"* (quartan); or on severity, like *"Teeksna"* (high fever); *"gambhir"* (malignant fever); *"Sannipata jwar"*, etc. *Abhinyas jwar* with slight or imperceptible rise of temperature is also described. There is also mention about the way fever can come down – by crisis or lysis.

How such accurate descriptions of fever were made long before the introduction of the clinical thermometer remains a matter of admiration and amazement. Sanctorius (1561 – 1636) of Padua designed the first clinical thermometer and a pulse watch. The mercury thermometer was the invention of Fahrenheit. The use of the clinical thermometer in the practice of medicine was introduced by his fellow Dutchman Hermann Boerhaave in 1709 and since that time the measurement of body temperature has been included as an integral part of the evaluation of most sick people. In 1865, Wunderlich wrote a monograph "On the temperature in Disease: a manual of medical thermometry". He said, "The more my observations were multiplied the more firmly rooted did my conviction become of the unparalleled value of this method of investigation as giving an accurate and reliable insight into the condition of the sick".

The Dread of Fever

Charaka Samhita states: "From among all disorders fever deserves to be described first, it being the foremost of all somatic diseases". It was

also recognized as the most important cause of death, and hence came to be associated with Shiva, the God of Destruction in Hindu mythology – fever being a manifestation of the anger of Shiva. In the Bible, fever was considered as a punishment by Jehovah of a frequently wayward people. Catastrophies not understandable by human wisdom were attributed to divine will or divine wrath or demoniacal influences. Smallpox in India has traditionally been attributed to the wrath of "Sitala Devi" and even today there is a temple in the city of Bombay presided over by this deity. The history of mankind is full of devastating epidemics characterised by fever. Malaria helped to complete the downfall of the Roman Empire. Of some 300,000 crusaders who left Western Europe in 1096 on the First Crusade, only 20,000 finally reached the Holy City, the rest perished through malaria. As late as the Second World War of 1939-45, the British and the Indian troops fighting in the eastern theatre were warned that enemy number one was malaria and enemy number two was Japan. Bubonic plague destroyed a third of the population of mediaeval Europe, creating economic and social chaos. Smallpox played a large part in the conquest of the New World by Spanish Conquistadors and English Puritans. Typhus killed 300,000 French soldiers in the Peninsular war and completed the ruin of Bonaparte's Moscow campaign. Yellow fever was a scourge which for generations wrought havoc and disrupted gigantic projects like the Panama Canal in this Century. Tuberculosis has been endemic throughout the history of mankind and has taken a large toll of human life. No wonder that early in the 20th century, Sir William Osler declared that, "of the three great scourges of mankind: fever, famine and war, by far the greatest, by far the most terrible is fever".

Mechanism of Fever

Fever remains a fascinating problem for both clinicians and basic scientists. In the wisdom of the body, does fever serve any beneficial purpose? The remarkable recent discovery by Kluger and his associates pertaining to the behaviour of infected lizards has thrown new light on this subject. Lizards must modify their body temperature entirely by behavioural means. When infected, they seek warmer environments that serve to raise their body temperature to febrile levels. Several other poikilotherms (including fish) behave similarly. The survival of infected lizards is directly correlated with the elevated body temperature. It has been shown by others that in febrile lizards a local inflammatory

response is rapidly mobilized at the infected site, and thus dissemination of the infection is markedly reduced.

Bacterial endotoxins (lipopolysaccharides from the bacterial cell wall) stimulate the biosynthesis and release by neutrophils and macrophages of a fever-producing agent. As little as 1 μg. of endotoxin from the typhoid germ can cause fever in man following its intravenous injection.

Recent evidence indicates that in response to a foreign invasion by microbes (and other kinds of insults to the body) the *activated macrophages*, the front-line bodyguards, produce a hormone-like agent "the leucocytic pyrogen", which acts on the thermoregulatory nuclei in the hypothalamus in the brain to produce fever. In the hypothalamus, this hormone seems to act by stimulating arachidonic acid release from its membrane-bound position in the cell wall, and thence the synthesis of prostaglandin E2 which has direct pyrogenic effects. Inhibitors of cyclo-oxygenase such as aspirin and indomethacin interfere with prostaglandin synthesis and thereby prevent the onset of fever.

It is now found that leucocyte pyrogen is identical with a factor that promotes lymphocyte proliferation, "lymphocyte-activating factor" (now collectively called interleukin-1). *In vitro* experiments have shown that both interleukin-1-induced T-cell proliferation and antibody production increase upto *twenty-fold* when the cells are cultured at febrile (39°C) rather than at normal (37°C) body temperature. It seems the temperature augmentation of antibody production is mediated by an early effect on Helper T-cells. Thus evolution seems to have built into a single hormone (interleukin-1) the ability, not only to stimulate vital defence mechanisms of cells against infection, but also to provide an optimal body temperature for these events.

Apart from *exogenous* activators (such as microbes) of the release of interleukin-1, there are *endogenous* activators such as several pyrogenic steroids (etiocholanolone) and urate crystals. Many malignant tumours (especially hypernephroma, carcinoma of pancreas, lung, bone and liver), Hodgkin's lymphoma and leukemias may present as fever. Myocardial, pulmonary and cerebral infarctions nearly always cause fever. Immunological injury almost always is febrile. Thyroid crisis and Addisonian crisis may be associated with fever.

Recent studies have implicated a number of brain peptides in the regulation of body temperature. In many instances, information is

lacking as to their specific locus and mode of action. Intracranial injection of TRH is associated with hyperthermia, whereas administration of an antiserum to TRH into the lateral ventricle is associated with a decrease in core body temperature. These effects of TRH are also observed in hypophysectomised animals, implying a central rather than a peripheral effect, secondary to increased thyroid hormone release. Hyperthermia induced by TRH is prevented by indomethacin, suggesting the involvement of endogenous prostaglandins which are thermogenic.

The current understanding about the mechanism of fever is depicted in Figure 10.1

Fever is a regulated rise in the body temperature which in human beings rarely exceeds 41.11°C (106°F) in contrast to the malignant hyperthermias caused by heat stroke or anaesthetic agents in which the temperature can rise to lethal levels. Fever above 106°F becomes life-threatening as the function of brain cells becomes suboptimal. Enzyme function comes to a halt when the body temperature exceeds 110°F and results in coma and death.

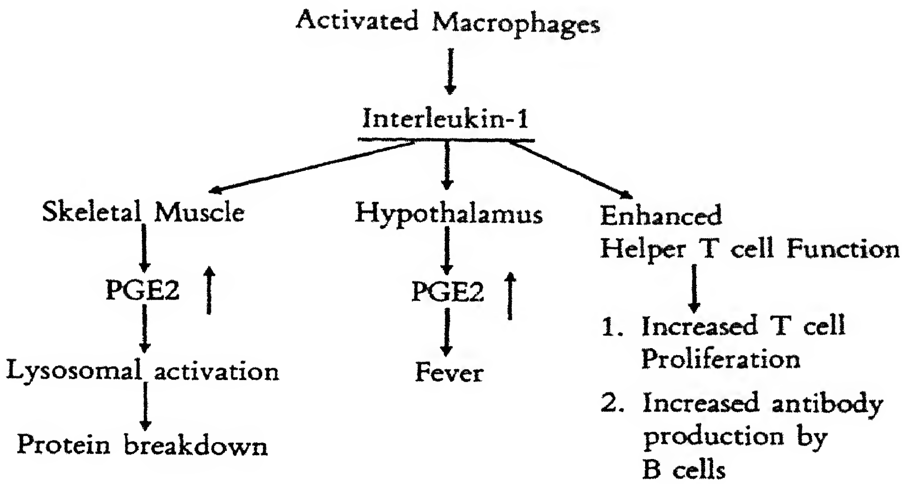
Effect of Fever on Muscles

Interleukin-1 not only acts on the hypothalamus to induce fever but also acts directly on the skeletal muscle to promote protein catabolism. The accelerated proteolysis (breakdown of protein) in muscles is part of an integrated physiological response of the host to infection, which provides precursors for gluconeogenesis or substrates for direct oxidation in view of increased metabolic needs and reduced food intake, and for the synthesis of acute-phase proteins by the liver, and for synthesis of immunoglobulins, and perhaps even for wound healing.

The muscle wasting in fever is described in Ayurveda.

It is interesting to note that although fasting or *"langhan"* was a common restriction in fever cases in ancient India, it was *prohibited* in a case of fever in which the physician saw a wasting process. One wonders if *Mahakalyanakaghruta,* a special preparation of ghee which was "recommended for kings", and claimed "to prove curative in all forms of fever", provided a source of high caloric diet and therby had a protein-sparing effect.

FIGURE 10.1



Genetic Syndromes with Fever

For the student of fever an intriguing disease is Familial Mediterranean Fever (FMF), an inherited disorder of unknown etiology, characterized by recurrent episodes of fever, peritonitis and pleuritis. Arthritis, skin lesions and amyloidosis are also seen in some patients. It occurs in patients of Sephardic Jewish, Armenian and Arabic ancestry. However, it has also been seen in patients of Italian, Askenazi Jewish and Anglo-Saxon descent as well as others. The demonstration that FMF is inherited as an autosomal recessive disorder has led to the thesis that it is another inborn error of metabolism, but no such error has been found despite extensive studies. Despite the severity of the symptoms during the attacks (abdominal pain, chest pain, joint pain) most patients are remarkably free from any debility during the intervals between attacks. With encouragement and an understanding of their disease, most FMF patients lead fairly normal lives. With the demonstration by Goldfinger in 1972 that *Colchicine* (used by mouth 0.6 mg. three times a day) dramatically reduced the number of attacks, the entire outlook of FMF has altered. The mechanism of colchicine's action in preventing FMF attacks is unknown.

Another interesting and important inherited disturbance of heat regulation is malignant hyperthermia (MH) characterised by a rapid

rise of temperature to 39 – 42°C (102 to 107.6°F), in response to inhalation anaesthetics such as halothane, methoxyflurane, cyclopropane, and ethyl ether or muscle relaxants, notably succinylcholine. The triggering anaesthetic releases calcium from the membrane of the muscle cell's sarcoplasmic reticulum, which is defective in storing this ion. The result is a sudden increase in myoplasmic calcium. The calcium activates myosin ATPase, which converts ATP (adenosine triphosphate) to ADP (adenosine diphosphate) and heat. There are also inhibition of tropanin, *uncoupling of oxidative phosphorylation,* activation of phosphorylase kinase and increased glycolysis. Muscular contraction occurs, and it as well as the chemical events, leads to the production of heat.

Phosphorylase A and adenyl cyclase are elevated in the muscles of MH patients, and provide useful biochemical markers of MH. In some patients, CPK may also be elevated but in many this test is entirely normal. Because of the tendency of this syndrome to run in families, its detection is essential. A thorough family history is the best way to avert problems during surgical anaesthesia. In susceptible patients, surgery should be performed under spinal, epidural, or regional anaesthesia. If this is not possible, a combination of pentothal and diazepam is probably safest.

Fever is one of evolution's most fascinating adaptations of the host to its environment. One might argue teleologically that the host, equipped with a physiological regulatory mechanism and the presumptive need for fever as long as infection lasts, has not required specific suppressor systems for survival.

To the doctor it also gives an important message: as long as the fever does not exceed dangerous limits the main emphasis should be *to find out the cause and treat it if possible.* When fever exceeds 105° then of course, bringing down the temperature itself becomes an important objective irrespective of the cause.

Ayurvedic Theories about Fever

Ayurveda describes *"Abhighat jwar"* (traumatic fever), that occurs as a result of the body being injured by weapons, brickbats, sticks, whips, teeth or by such other external agencies.

In Viman Sthana, Chapter 3, while discussing epidemics that decimate populations (*"Janapadodhwansa"*) Agnivesha queries: "But how does the simultaneous destruction of communities, constituting

as they do of individuals who differ from one another in constitution, diet, physique, vitality, habits, psychic make up and age, take place by the incidence of *one single disease?"*

Atreya explains: "Though a community may be heterogeneous in respect to constitution etc. of its individual members, there are *other common factors* which being adversely affected will cause simultaneous outbreak of diseases having similar symptoms. It is these common factors – *winds, waters, the country and the seasons,* that devastate the populations."

"A season exhibiting unnatural or contrary features, affects or reverses the natural properties of water and vegetables, which when drunk or eaten cause dreadful epidemics. The best safeguard lies in not using such defiled water and vegetables when an epidemic breaks out".

"Some times pollens of poisonous flowers and grasses wafted by the winds, invade a town or a village and produce a sort of epidemic cough, asthma, catarrh and fever *irrespective of all constitutional peculiarities".* Although this description mentions pollens and grasses it probably does not indicate allergy since it emphasizes the effect on the people irrespective of all constitutional peculiarities. It may well be a description of epidemic influenza.

"Towns and villages are known to have been depopulated through malignant astral influences, or through houses, wives, beds, seats, carriages, riding animals etc."

"In such cases migration to a healthy or unaffected locality may prove beneficial to the affected community".

Charaka mentions countries which abound in *mashaka* (mosquitoes), *mooshaka* (rats) and *makshika* (flies) as unhealthy.

In *Charaka Samhita,* in the Sutrasthan, Chapter 30, it is stated that "unsalutary *winds,* unsalutary *water,* unsalutary *country* and unsalutary *seasons* are the cause of catastrophies". Water is considered to be more important than wind, and country more important than water and season yet more important than country, by virtue of their degree of indispensability. In this statement one can see the rudimentary concept of germ theory of disease and the concept of epidemiology. Both microbiology and epidemiology blossomed into major scientific disciplines two thousand years after Charaka and Sushruta, in the 19th century.

For those fevers which had characteristic clinical features and striking external manifestations like the skin rash of smallpox, chickenpox and measles, clinical characterization was relatively simple. But when the fever presented with no characteristic symptoms or physical signs, the identification of the causative agent becomes difficult. Physicians worked under this handicap till the 17th century.

From the description of *vataja* fever, *pittaja* fever and *kaphaja* fever in *Charaka Samhita,* it is difficult to make an etiological diagnosis as we understand today. One can speculate that *pittaja fever* characterised by "high fever with perspiration, vomiting and diarrhoea, yellowness of eyes, stools and urine, delirious talk and loss of consciousness" refers to *viral hepatitis,* or less likely, amoebic liver abscess following amoebic dysentery. Some descriptions are suggestive of encephalitis and meningitis, diphtheria, malaria, otitis media and typhoid fever.

Help of Drugs to Differentiate Fevers

A major step in the differentiation of causes of fever came by accident. A Jesuit Father, working among the Peruvian Indians in the high Andes was attacked by feverish ague (malaria). The local Inca medicine man gave him a bark tea. He recovered, and having failed to persuade the medicine man to part with the secret of the remedy, he discovered how the bark was obtained and smuggled some supply back to Lima.

A romantic embellishment of the legend is the story of the beautiful countess of Cinchona, wife of the royal Governor of Peru, who recovered from her fever with this bark remedy. Spoil-sport historians have proved that the countess of Cinchona never went to Peru and never had fever and consequently never needed the fever bark, but the legend was perpetuated forever. Linnaeus, the great Swedish botanist accepted it and classified the fever bark tree as Cinchona after her.

Quinine, tincture of Cinchona bark was introduced into Europe in 1632. It has been said aptly, "Quinine did for medicine what gunpowder had done for war". Like all new discoveries, quinine was abused. It was regarded as a cure-all and prescribed for diseases for which it had no value, and was given in excess with ill effect. Thomas Sydenham (1624-1689) used it wisely and *used its response as a criterion to separate malaria from a host of other fevers.* Sydenham maintained that every disease belonged to a certain definite species, which could be described and classified, just as a botanist does plants. Sydenham's studies of the geography and meteorology of epidemic diseases and

how they recovered periodically were the basis of modern epidemiology. Sydenham also used the response to colchicine to differentiate gouty arthritis with fever, from other arthritides.

On June 2, 1763, a paper entitled "An account of the success of the bark of the willow in the cure of agues" was read to the Royal Society of London. The author Reverend Edward Stone recommended a decoction of the bark of the white willow (salix alba vulgaris) for treating "aguish and intermitting disorders", a description of malaria. Two coincidences bolstered Stone's proposal to try willow bark against malaria. First, the bark tasted extraordinarily bitter, as does Cinchona, the Peruvian bark, that was by then already acknowledged to be the sovereign remedy for malaria. Second, the willow grows in damp and marshy places, which in Stone's days were often malarial and where in accordance with the contemporary medical doctrine, he would have expected to find a cure for the disease.

Stone's decoction did indeed relieve the feverish symptoms of malaria, because, as chemists were to learn later, it contains *salicylic acid,* an antipyretic compound. It did not cure malaria, however, because willow bark does not contain quinine, the ingredient in Cinchona bark that acts directly against the malaria parasite. Stone's recommendation of willow bark, unfortunately led to the adulteration of Cinchona bark with a less curative (and less expensive) material.

In 1829, a French pharmacist, H. Leroux, isolated from a willow bark extract *Salicin,* a compound of glucose and salicyl alcohol. Salicylic acid itself was derived from this compound in 1838 by Raffaele Piria of Naples, three years after Lowing had extracted the same acid from meadow-sweet flowers. In 1842, William Proctor of USA and Auguste Cahours of France obtained methyl salicylate from oil of wintergreen; Cahours later carried the isolation further to salicylic acid. Since then the chemical relatives of salicylic acid have turned up in many plants. A salicylate has also been found in the secretion of the beaver's prepuce, that is known as castoreum; the substance is perhaps derived from the bark of trees on which beavers subsist. It would be interesting to study the Ayurvedic *jwaraghna* (antipyretic) herbs for salicylate content.

The purification and identification of salicylates occurring in nature facilitated their synthesis in the laboratory. In 1852, H. Gerland synthesized salicylic acid and by the end of the decade in 1860 Hermann Kolb and E. Lautemann had developed a practical method of preparing it synthetically from phenol in sufficient quantity for therapeutic use.

As chemists had been encouraged to synthesize salicylates by reports of medical interest, physicians were now aided in their research by the availability of salicylic acid and its purified esters. Although salicylic acid was probably the wonder drug of its day, its success was diminished by the irritation and damage it caused to the lining of the mouth, food pipe and stomach. The molecule of the acid contains a hydroxyl (OH) group and a carboxyl (COOH) group. The replacement of the hydrogen atom of the carboxyl group with a metal such as Sodium, results in a salt, Sodium Salicylate, which is less irritating than the acid. Sodium salicylate was first used as an antipyretic by Buss in 1875.

In 1876, more than a century after Stone's communication to the Royal Society, a Scottish physician MacLagan echoed Stone's original proposal: "Nature seems to produce the remedy under climatic conditions similar to those which give rise to the disease—among the Salicaceae I determined to search for a remedy for acute rheumatism".

MacLagan in 1876 was the first physician to treat rheumatic fever successfully with salicylates. In the following year Germain See announced in Paris that salicylates also relieved chronic rheumatoid arthritis and gout. Just as therapeutic response to quinine helped to determine malaria as the cause of the fever, therapeutic response to salicylates helped to determine rheumatic fever as the underlying cause. Rheumatic fever could be separated from rheumatoid arthritis by the other clinical features. Response of colchicin characterized the gouty arthritis as distinct from the other types of arthritis. Felix Hofmann, a Bayer chemist, produced Aspirin (acetyl salicylic acid) which was introduced into medicine in 1899 by his colleague Heinrich Dreser. The synthetic salicylates soon completely displaced the more expensive compounds obtained from natural sources. The mechanism of action of aspirin-like drugs became clear only in 1971, as inhibitors of prostaglandin synthesis.

Fever and Sepsis

Infection of wounds was observed since antiquity and people in all ages had vague concepts about "poisonous miasma" in the air. Antony van Leeuwenhoek had in 1676, reported on his observations of "an incredible number of little animals of diverse kinds" through his microscope. These were micro-organisms but he had no idea of their relationship to infection. Long before Pasteur showed the existence of bacteria, many observers had suspected the method of spread of wound infection and thought of a means to prevent it.

A notable example was the dreaded *puerperal fever*, an infection of the genital tract often fatal to women after child birth. Puerperal fever had been noted as a risk attending the birth of a child from ancient times, but never on a large scale.

It seems something of a paradox that danger to the mother resulting from puerperal fever should have coincided with the custom, beginning in the Sixteenth Century, of the physician attending confinement, rather than the midwife. As time went on, the development of hospitals and the increased use of lying-in wards appeared to aggravate the situation rather than improve it.

Between 1650 and 1850 Europe was ravaged by some two hundred epidemics of the disease. The worst being in 1773 in the Lombardy region of Italy when, during the course of twelve months, not one woman lived after delivering her child. No one took notice of the fact that women giving birth in their own homes were much less likely to contract the illness than those confined in hospitals, though the hospital was intended to provide care and comfort and to ease the pangs of labour. In 1773, Charles White of Manchester stressed the need for strict cleanliness and adequate ventilation in the birth room. In 1843, Oliver Wendel Holmes in Boston aroused widespread antagonism in his medical colleagues when he again suggested that dirty hands in midwifery caused many deaths. He recommended a complete change of clothing before conducting a delivery. He remarked "medical logic does not seem to be taught or practised in our medical schools".

In 1847, Ignaz Philipp Semmelweiss (1818 – 1865), a Hungarian doctor at the maternity hospital in Vienna noted that of the two obstetric clinics in his hospital, the one which had a high death rate from puerperal fever was the one visited by medical students directly after work in the dissecting room, without washing their hands. In the other obstetric ward, staffed by midwives who washed their hands before deliveries, the death rate was much lower. In 1847, a great friend and colleague of Semmelweiss, Kolletscha, died from an infection sustained by pricking his finger at a post-mortem examination. Semmelweiss observed that the fatal symptoms of his friend were similar to those that he had observed in puerperal fever. He posted a notice at the entrance to the clinic ordering all students and doctors coming from the post-mortem room to *wash their hands* in a basin of chlorinated water (chloride of lime). In a few months the death rate among the mothers dropped by 75 per cent and in two years by 90 per cent.

It might have been thought that this all important discovery by Semmelweiss would have been welcomed by his contemporaries. But it was not so. His superiors at the hospital put it as a coincidence and insisted that puerperal fever was a natural phenomenon. There were fierce protests against his "interference" and eventually he was driven from Vienna to his native Hungary.

While Semmelweiss was facing oppostion in Vienna to what seemed as a perfectly logical theory, in other parts of Europe, obstetricians and surgeons were realising the value of absolute cleanliness in operations, though the reasons for it were by no means apparent. In London, Sir Thomas Spencer Wells, the most eminent surgeon and an early pioneer in the removal of ovarian tumours, had an astonishingly high success rate which he attributed to his absolute insistence on cleanliness.

It was a brilliant chemist, Louis Pasteur (1822 – 1895) who vindicated Semmelweiss. Pasteur extended his work on fermentation by yeast to the study of airborne micro-organisms. Joseph Lister (1827 – 1912), Professor of Surgery at Glasgow read Pasteur's researches in bacteriology and realised for the first time that sepsis was caused, not by the air itself but by the germs it contained. Pasteur had shown that these could be destroyed by heat, filtration or antiseptics. To Lister, the last offered the best protection for a surgical wound. He decided to use the disinfectant carbolic acid which the town of Carlisle had just used to disinfect its sewage. His first experiment was only partly successful since the acid burned the patient's skin. In subsequent experiments, Lister applied a solution of carbolic acid to wounds, his hands, his instruments and to his dressings. To kill germs in the air he devised a spray which pumped carbolic acid into the area where the operation took place. Using these new methods, surgery became safe, in striking contrast to the earlier conditions wherein "a man laid on the operation table was exposed to more chances of death than a soldier on the battle field".

Lister was derided by his colleagues (as is always the experience of pioneers) but his recoveries contrasted so conspicuously with their losses that his example prevailed. Today asepsis is attained by passing only filtered air in the operation theatre, sterilization of air by ultraviolet lamps, sterilization of clothing, dressings and instruments and scrupulous cleanliness of the human personnel.

Birth of Medical Microbiology

Robert Koch, a country doctor in Germany was concerned about the havoc which a disease called "splenic fever" was causing among the

sheep and cattle of the farming community. By most ingenious methods devised in a home-made laboratory, Koch was able to prove that a large square-ended rod was constantly present in the blood of animals dying of splenic fever, that this microbe could be grown and purified from contaminants on nutrient jelly, and when injected into laboratory animals could reproduce an infection identical with that which killed the cow and the sheep. This was the first wholly satisfying evidence that a specific germ, the anthrax bacillus, was the cause of a specific disease. And thus, by 1880 the new science of microbiology was firmly founded and its importance in the economy of men, animals and industry was beginning to be appreciated. Over the next two decades a variety of pathogenic specific bacteria (cocci, bacilli, vibrios, spirilla, spirochetes) and fungi, and rickettsia and viruses were identified.

Pasteur was the first to extend Jenner's *protective vaccination* by the use of living attenuated cultures of pathogenic microbes against important infections like anthrax, swine erysipelas and chicken cholera, and today the attenuated vaccine is being used with outstanding success in such diverse diseases like poliomyelitis, yellow fever, measles, diphtheria and tuberculosis, rabies and tetanus.

The demonstration of bacterial toxins by both French and German scientists was the precursor of antitoxin therapy. In 1890, Behring and Kitasato published a report in which they demonstrated that animals made immune to an infection developed a neutralizing principle in their serum. These observations created enthusiasm to isolate and identify the neutralizing principle. Later on the inoculated substance that evoked an immune response was termed *antigen,* and the serum neutralizing principle, the *antibody.* Von Behring's work led on to Ehrlich's concept of "magic bullets" and so to modern chemotherapy.

Evolution of Chemotherapy of Infection

With the knowledge of bacterial and protozoal causation of diseases and the development of techniques for infecting laboratory animals, scientific therapeutic experiments could be performed. The differential staining of tissues and bacteria by dyes used for microscopical techniques, gave Paul Ehrlich (1853 – 1915) the idea that aniline dyes used for staining bacteria, could be used for killing them as well. In 1891, he cured experimental malaria in guinea pigs with methylene blue, but it was less effective than quinine. In 1904, he controlled trypanosome (African Sleeping Sickness) infections in mice with another dye, trypan red, but it was ineffective in other species.

Ehrlich coined the word "Chemotherapy". In 1906 he wrote: "In order to use chemotherapy successfully we must search for substances which have an affinity for the cells of the parasites and a power of killing them greater than the damage such substances cause to the host organism so that the destruction of the parasite will be possible without seriously hurting the host. This means we must strike the parasites and parasites only, if possible, and to do so, we must learn to aim, learn to aim with chemical substances!"

By 1906, it was clear that chemotherapy was a practical proposition, and not the fantasy that eminent contemporaries declared it. Inorganic arsenicals had been shown to clear trypanosomes from the blood of infected horses and an organic arsenical had been used successfully on man. This inspired Ehrlich to make and test further compounds. His efforts resulted in the introduction of arsphenamine (salvarsan) for the treatment of syphilis and it was soon followed by neoarsphenamine (Neosalvarsan) which was widely used until 1945 when it was superseded by penicillin.

After neoarsphenamine there was a lull. Then the antimalarial pamaquin and mepacrine were developed from dyes and in 1935 the first sulphonamide linked with a dye (Prontosil) was introduced as a result of empirical experiments by Domagk, for which he was awarded the Nobel Prize in Medicine in 1938.

The Advent of Sulpha Drugs and Penicillin

"For those who did not enter medical practice until the end of the 1930's it is difficult to imagine the devastating uncertainty in life produced by lobar pneumonia", writes Sir Harold Himsworth. In different epidemics the mortality ranged from 5 to 25 per cent. In the spring of 1937, a new drug called M. & B 693 (the code number given to Sulphapyridine by its industrial developer, May and Baker) and its effect on patients of pneumonia was "something that no human being had ever seen before". It was a dramatic example of curative drug therapy, and took away the dread from lobar pneumonia, described by Sir William Osler as "the captain of the men of death". Lobar pneumonia in a previously healthy person no longer carries the distress and risk that it did, with the anxious wait for upto ten days for the "crisis" when the fever dropped dramatically as the immune response of the body at last killed the invading bacteria. The results obtained by sulphonamides in puerperal sepsis and meningitis were also dramatic. In general, the sulphonamides exert only a bacteriostatic effect in the

body, and cellular and humoral defence mechanisms of the host are essential for the final eradication of the infection.

In 1928, seven years before the discovery of the sulphonamides, Alexander Fleming (1881 – 1955), a London microbiologist, whilst studying staphylococcal variants found one of his cultures plates contaminated with a fungus which destroyed surrounding bacterial colonies. This accidental discovery led Fleming to investigate the properties of "mould broth filtrates" which for brevity he named "penicillin". He described penicillin as an antiseptic more powerful than carbolic acid (phenol) which yet could be safely applied to the tissues. Here was an *antibiotic,* a substance produced by living organisms, that also kills organisms at high dilution. In 1939, principally as an academic exercise E. B. Chain and H. W. Florey in Oxford undertook a new investigation of antibiotics. They prepared penicillin, discovered that it was effective if introduced into the blood as well as when applied to local surface infections in mice, and confirmed its remarkable lack of toxicity. At the time of this discovery—July, 1940, Britain was being bombarded from the sky. Results of a small clinical trial in 1941 were good and it was clear that penicillin might have military importance but large scale production in Britain at that time was not possible. The USA was still at peace, so arrangements were made for large scale production of penicillin there and ample supplies were available to treat casualties in the later part of the war. Although numerous other antimicrobial agents have been produced since penicillin became available, it is still a widely used, major antibiotic and new derivatives of the basic penicillin nucleus are being produced every year. Many of these have unique advantages, such that members of this group of antibiotics are presently the drugs of choice for a large number of infectious diseases.

Since 1939 large programmes of screening fungi and bacteria for antibiotic production have been conducted. The first success was the isolation of streptomycin from a soil organism (streptomyces) and this was followed by the tetracyclines, erythromycin and others. Simultaneously there have been developments in synthetic agents, especially against tuberculosis (INAH, PAS, pyrazinamide, thiacetazone, ethambutol) and tropical diseases including malaria, leprosy and amoebic dysentery. That nothing is beneath the notice of investigators is illustrated by the discovery of antibacterial substances in the anal gland secretion of the Argentine ant and in the faeces of blow-fly larvae.

Most important microbial infections are now treatable. Prominent exceptions include small viruses. Viruses enter host cells and grab host machinery to multiply there so that selective chemical attack is specially difficult. However, substances capable of preventing the *viral entry* into the host cell have been found out and offer prospects of effective prevention. For example human influenza virus infection can be *prevented* by *amantadine,* a synthetic tricyclic amine of unusual structure unrelated to that of any other antimicrobial agent.

The Biochemical Basis of Antibiotic Action

All antibiotic substances depend for their effect on an ability to inhibit a biochemical process or disrupt a vital cell structure in an invading organism, without having a significant effect on the host. The best antibiotics approach this ideal behaviour closely, and many antibiotics inhibit biochemical reactions or disrupt cell structure or functions which do not occur in the host cell at all. For example penicillins and Cephalosporins inhibit bacterial cell wall synthesis, and mammalian cells contain no equivalent structure. Similarly polymyxin disrupts the structural integrity or biosynthesis of the bacterial cytoplasm membrane, and this structure also seems to differ in significant respects from the membranes in mammalian cells.

In many cases, however, an antibiotic relies for its action on having a greater effect on some biochemical reaction in the invader than in the host. Such differential effects can arise in a number of ways; in some cases the relevant enzyme in the host has a lower affinity for the inhibitor and thus is less sensitive at low concentrations. Some times the enzyme is present in much larger amounts in the host and therefore less sensitive to complete inhibition; but in other cases the host enzyme is relatively inaccessible to the inhibitor because of the intervention of one or more permeability barriers.

Another type of differential sensitivity, which is less commonly met with in the action of antibiotics than in the action of chemotherapeutic agents, is caused by the ability of the host, but not the invader, to satisfy its requirement for a given metabolite by using a collateral biosynthetic pathway. In this case, addition of the inhibitor blocks the target enzyme in both host and invader, but the essential product of the inhibited reaction is provided by the alternative route in the host cell alone.

Whatever the biochemical basis of these differential effects, some of which are extremely subtle in operation, such a differential between

host and invader is an inescapable necessity for successful antibiotic action.

An illustrative example will make this point clear.

Piperazine hydrate is effective against ascaris lumbricoides (round worms) and enterobius vermicularis (thread worm) and acts by paralysing the worms by curare-like action at the myoneural junction so that they are expelled alive by peristalsis. The curare-like action is extremely weak on mammalian skeletal muscle.

Rheumatic Fever

Over the centuries few diseases of childhood have induced a greater feeling of helplessness among physicians or aroused more concern in the families of patients than rheumatic fever. Although the acute symptoms such as the swollen, tender joints for which the disease was named were disturbing, it was known that they usually subsided without producing any permanent disability. Rheumatic involvement of the heart, on the other hand, sometimes brought sudden death in a fulminating attack and more often led to chronic heart disease. To this day the menace of rheumatic fever in India continues to take its toll as measured in terms of the scarred heart valves produced by it, which eventually impair cardiac function leading to premature death.

In the past sixty years, rheumatic fever has been extensively investigated. It has been the focus of a host of clinical investigations and has stimulated fundamental studies in immunology and microbiology. By now it is clear that streptococcal infection may lead to rheumatic fever, but the exact mechanism eludes us.

For many centuries rheumatic fever was a totally baffling disorder. Then in the 19th century, physicians began to note that acute rheumatism was often preceded by a septic sore throat or by scarlet fever. When early in this century streptococci were shown to be the agents responsible for many cases of tonsillitis and for scarlet fever, the way was opened at last for systematic investigations into the cause of rheumatic fever. A particular group of the haemolytic streptococcus, known as Group A is clearly implicated in the development of rheumatic fever, which can be prevented by vigorous treatment of streptococcal infection with such antimicrobial agents as penicillin.

The natural history of rheumatic fever supports the concept that this disease may be the result of a state of *hypersensitivity*. Hypersensitivity is a special form of the immune reaction, a process by which the body

combats the intrusion of foreign substances or antigens, by synthesizing specific antibodies directed against them. The interval between the streptococcal infection and the onset of rheumatic fever is about equal to the time required for an antigenic stimulus to provoke a maximal antibody response. The typical pattern of the rheumatic attack – a latent period during which the patient shows no signs of illness, followed by the sudden development of fever and joint pain—is quite similar to the pattern in acute *serum sickness,* a disorder in which sensitivity to an antigen is well established. Patients who have rheumatic fever show a greater outpouring of streptococcal antibodies, on the average, than those who have a streptococcal infection without rheumatic fever. Histological examination of rheumatic lesions reveals changes very similar to those obtained in experimental hypersensitivity in animals.

In 1962, Melvin Kaplan of the Western Reserve School of Medicine in Chicago, U.S.A. reported the existence of an immunological cross-reaction between Group A streptococci and cardiac muscle. In this experiment, streptococcal membranes are injected into a rabbit. The globulin fraction, containing antibody formed against the membranes, is isolated from the rabbit's blood, and coupled to a fluorescent compound. When the fluorescent antibody is tested on streptococci, it reacts with antigen in the bacteria, so that in spite of washing it remains bound to the bacteria, which glow under ultra-violet radiation. Tested on heart muscle, the antibody reacts in the same way. It does not react with other tissues, nor do antibodies to other bacterial species react with the heart muscle. If instead of rabbit globulin we test globulin from patients with rheumatic fever, we get similar results.

Hence the current hypothesis is that because of the immunological cross-reactivity between the streptococcal membrane antigens and myocardial sarcolemma, an assault on the streptococcal antigen inadvertently becomes an assault on the "self-antigens", a kind of autoimmune disease.

Fever is an important feature of another autoimmune disease, systemic lupus erythematosus (SLE). It is interesting and important to note that certain drugs (INAH, PAS, dilantin, methyl dopa and levodopa, phenothiazines) have led to SLE-like syndrome.

Drug Fever

One cannot end the discussion about fever without emphasising a 20th century cause of fever, namely *drug fever.* A careful history of drug intake should be taken in every patient with unexplained fever. Fever

due to allergy to one of the antibiotics may become superimposed on the fever of the infection for which the drug was given, resulting in a very confused picture. Any drug can theoretically act as a hapten, which combining with a body protein becomes an immunogen. Common drugs causing fever include sulphonamides, barbiturates, laxatives, particularly phenolphthalein, iodides, thiouracil. Any question of drug fever can be resolved rapidly by stopping all drugs, and watching the response. If the fever comes down, presumably it was a drug fever. Alternatively, it could be a coincidental happening that the fever came down. The point could be proved by giving a challenge of the suspected drug again after fever has subsided and showing the recurrence of fever, but in actual practice this is hardly ever done for fear of causing unpleasant or even dangerous reaction.

Present-Day Diagnosis of Fever

Since the commonest cause of fever is infection, the effort in diagnosing it requires the direct or indirect demonstration of a pathogenic microbe on or within the tissues of the afflicted host. The direct microscopic examination of body fluids, exudates and tissues is extremely helpful as for example examination of thick and thin blood smears for malaria parasites, and examination of sputum for tubercle bacilli, and examination of urethral smear for gonococci.

Immune microscopy combines the specificity of immunologic procedures with the speed of direct microscopy. In the immunofluorescent technique, smears thought to contain viral, bacterial, fungal or parasitic organisms are stained with specific antibody preparations labelled with flurorescent compounds and examined with a fluorescent microscope.

Enzyme-linked-immunoadsorbent assay (ELISA) tests are similar to the immunofluorescence test except that the antiserum is reacted with an enzyme-labelled anti-species conjugate. After treatment with an appropriate substrate, a colour change can be visualised with the ordinary light microscope, obviating the need for expensive fluorescent microscopy.

The electron microscope has been useful in the identification of certain viruses which do not produce cytopathic effects in cell cultures (the usual method of detecting the presence of the virus). It has been particularly valuable in the detection of *rotaviruses* in the stool specimens of infants and small children suffering from gastroenteritis.

A variety of immunological techniques have been introduced for the rapid detection of microbial antigens or their by-products. The counter

immunoelectrophoresis (CIE) is a widely used technique. The specimen being tested for the antigen is placed in an agar well and specific antiserum in a second opposed well. An electric current is then passed through the agar resulting in rapid confluence of antigen and antibody with the formation of a precipitant within a matter of minutes.

Radioimmunoassay (RIA) techniques have been used for the detection of the Hepatitis B surface antigen associated (HBs Ag-associated) infection and in the prevention of such infections by screening blood and blood products for the presence of antigen. Experimental RIA procedures have also been developed for mycobacteria and fungi.

The isolation of the etiologic agent by culture in artificial media, tissue cultures, or animals, is generally the most definitive means of diagnosis of an infectious disease. Throat swab, sputum or endobronchial aspirates, urine, blood and CSF are commonly used for culture. Additional advantage of culture is the ability to provide information about sensitivity to various antibiotics so as to make an appropriate choice.

Immunologic methods are intended to supply evidence of past or present infection by demonstrating antibodies in serum or other body fluids, or indicating changed reactivity of the host (hypersensitivity, allergy) to products of the organism.

Problems and Failures of Chemotherapy

With the vast array of chemotherapeutic and antibiotic agents available to us today, there are few organisms that are not sensitive to some antibiotic. Despite this seemingly comfortable position, a large number of patients continue to develop infections and many continue to die from them. In these patients our drugs seem to have failed. Often this failure is more apparent than real and may be attributable to one of several causes, including the following:

1. Failure to adjust the proper dose of the antibiotic and giving inadequate doses.
2. Inappropriate use of antibiotics when not needed as in viral infections or non-infectious causes of fever such as SLE, or autoimmune disorders, or malignancy.
3. Failure to remove obstruction to hollow viscera or to drain purulent material.
4. Superinfections due to resistant organisms.
5. Defects in host resistance—imunologically compromised host.

All effective remedies are double-edged weapons, hence one should be mindful about the potential to do harm as well as the potential to do good. Adverse effects of drugs can be death (penicillin: anaphylaxis; chloramphenicol: aplastic anaemia; sulphonamides: agranulocytosis etc.), permanent disability or recoverable illness.

A responsible physician will always weigh the benefits and risks of drugs including sulphonamides and antibiotics and decide if the benefits are overwhelmingly greater than the risks, and, equally important, the *risks* of *not giving the drugs.* The last consideration escapes the minds of critics of modern medicine. In their fear of penicillin and chloramphenicol, many otherwise intelligent and rational persons go to the irrational extent of denying the benefits of these drugs when they are clearly indicated. One has only to remember the death toll due to lobar pneumonia and typhoid before the advent of penicillin and chloramphenicol respectively and the sea change brought about by these two drugs in the outcome of these two diseases. There are many responsible citizens who take the irresponsible attitude about these drugs. The only answer to this situation is more responsible action on the part of the medical profession (scrupulously avoid the misuse of antibiotics) and public education which should make them aware, not only of the risks of drugs but also in certain well-defined situations, the risks of not giving the drugs.

The Problem of Resistant Microbes

Little by little we are experiencing the erosion of the strongest bulwarks against serious bacterial infections in the modern antibacterial era.

When the sulphonamide drugs were introduced they were widely and successfully used in the treatment of gonorrhoea and of group A hemolytic streptococcal infections. In gonorrhoea, resistance first emerged and was spread rapidly by both patients and their contacts to a varying and sometimes large number of other contacts. The almost universal use of sulphonamides in the prophylaxis of streptococcal infections and rheumatic fever resulted in the emergence and rapid spread of two resistant strains (Types 17 and 19) which then gave rise to extensive and serious epidemics of highly fatal streptococcal pneumonias and empyema.

In both of these situations the subsequent availability and general use of penicillin provided the needed effective therapy and prophylaxis. In gonorrhoea, however, the originally marked suspectibility of the

organism declined rapidly and ultimately resulted in strains totally resistant to penicillin by virtue of producing penicillinase.

Meningococcus which was originally highly sensitive to sulphonamides became gradually resistant during the 1960's, rendering the sulpha drugs unreliable and ineffective for therapy as well as prophylaxis of that infection.

Penicillin was initially highly effective against staphylococcus aureus infections. However, the organism producing penicillinase soon appeared resistant to penicillin and such resistant strains replaced susceptible ones in hospitals where penicillin was extensively used. With the introduction of methicillin and other penicillinase-resistant penicillins and later the cephalosporins, this problem was alleviated. However, methicillin-resistant staph-aureus have now emerged.

Strains of staphylococcus aureus that are inhibited by normally low concentrations of penicillin and other antibiotics but are not killed by very high concentrations have been described and labelled "antibiotic tolerant", result of a deficiency in the autolytic enzymes required for the lysis of the organism. Pus from pneumococcal empyemas has been shown to inactivate penicillin rapidly.

Recently strains of Hemophilus influenza Group B producing penicillinase and being resistant to ampicillin have occurred. Other strains resistant to chloramphenicol have appeared.

Epidemics of typhoid fever due to Salmonella typhi resistant to chloramphenicol, the drug of choice for this infection, occurred in Mexico and Vietnam a few years ago. Fortunately such cases responded to either ampicillin or trimethoprim-sulfamethoxazole.

Another worrisome development is the increasing occurrence of multi-resistant gram-negative rods and the increasing incidence of Mycobacterium tuberculosis resitant to the "first line" drugs isoniazid and streptomycin and to several "second line" drugs, including rifampicin,

Recently, pneumococci resistant to penicillin and multi-antibiotic resistant have caused outbreaks in South Africa.

Continuing Battle against Infection

Developments in sanitary engineering, vector control, immunization and specific chemotherapy have modified the situation favourably in man's age-old battle against biological agents of disease—viruses rickettsias, bacteria, mycoplasma, chlamydia, fungi, protozoa or

nematodes. Despite the elimination of some infectious diseases like smallpox and the profound reduction in the morbidity and mortality rates of many major infections, human race is by no means free of infection. As some important infectious agents have been controlled, others have emerged as troublemakers. The use of cytotoxic drugs for malignancy, immuno-suppressive drugs to control rejection of organ transplants, the insertion of prosthetic devices into the blood stream, and the progressive longevity of people with chronic degenerative diseases, have brought in their wake *opportunistic infections* due to organisms which are harmless commensals for healthy individuals. Another problem is *superinfection*, caused by micro-organisms that are resistant to the drug that was given for the original infection. Furthermore antibiotics may select out resistant variants or facilitate the transfer of resistance (R) factors between pathogenic and commensal enterobacteria. New enemies are being discovered like *Legionella pneumophilia* causing pneumonia, first described in 1976 and a tick-borne *spirochetosis* causing Lyme arthritis described in 1982.

Old enemies are appearing in new manifestations such as the toxic shock syndrome (TSS), a newly described clinical entity with serious morbidity affecting primarily menstrual-age women. Fever, hypotension, skin rash, vomiting, diarrhoea, myalgia, hepatic and renal involvement lead to a mortality rate of 10 – 15 per cent. The causative organism is the age-old *Staphylococcus aureus*, with *toxins*, pyrogenic exotoxin C and enterotoxin F, quite distinct from previously characterized staphylococcal toxins. One brand of vaginal tampon, statistically associated with TSS (which occurred mostly in previously healthy young women who became ill during the first few days of menstrual cycle) was withdrawn from the market, following which the number of reported cases decreased dramatically.

Male homosexuals and drug addicts in USA have recently been the victims of multiple infections with viruses (CMV and herpes simplex), bacteria (M.tuberculosis, M. avium intracellular), parasites (pseumocystis carinii) and fungi (cryptococcus neoformans & candida albicans) and some of them subsequently developed Kaposi's sarcoma. It is postulated that acquired immunodeficiency (AID) makes these patients particularly vulnerable.

In our battle for survival, we have to be eternally vigilant. Organisms that seem to have little biological significance at present may assume practical importance in future, as the experience with Legionnaire's disease has revealed.

Chapter 11

WISDOM OF THE BODY

Introduction

In 1923, the late Professor E. H. Starling, of University College London, gave the Harveian Oration before the Royal College of Physicians, which he entitled "The Wisdom of the Body". Starling spoke admiringly about the marvellous and beautiful adjustments in the body that maintain its steady state. "Only by understanding the wisdom of the body", he declared, "shall we attain that mastery of disease and pain which will enable us to relieve the burden of mankind".

The idea that disease is cured by natural powers, by a *vis Mediatrix naturae,* is an ancient one, held by Hippocrates (460—377 B.C). It implies the existence of agencies and mechanisms within the body which are ready to operate correctively when the normal state of the organism is upset. This idea was succinctly put by Claude Bernard in 1857: "The constancy of the internal environment is the condition of free and independent life". According to J. S. Haldane, no more pregnant sentence was ever framed by a physiologist. The American physiologist Walter Cannon in 1929 coined the word *"homeostasis"*, to describe the coordinated physiological processes which maintain the steady state. Bernard listed water, oxygen, uniform temperature and nutritional supplies including glucose, salts and fats as the necessary constants. To these one would now add pH and osmolarity. For example heavy physical exercise raises the temperature of the blood and also its acidity. A meal raises the concentration of blood glucose, and drinking water lowers its osmolarity. Exercise, food and drink each initiate responses which cause the blood to return to the normal state.

Stability of the Internal Environment

The blood and the lymph which bathe the cells are conceived of as an internal environment which protects the cells of the organs of the

body from variations in the external environment which is always changing. J Barcroft and J. S. Haldane in England, and L. J. Henderson and W. B. Cannon in U.S.A. were four great physiologists, who in the first quarter of the 20th Century developed Claude Bernard's conception of the stability of the internal environment. Few men have submitted their bodies to severe environmental stress in the interest of physiology as frequently as did Sir Joseph Barcroft. He pointed out that most essential functions of the body can proceed over a fairly wide range of conditions but the mental processes are much more restricted. A small change of hydrogen ion concentration in the blood over a short period of time can affect the higher nervous system causing inability to concentrate, which may last for two or three days. Most of us have experienced how a trivial degree of fever can seriously impair mental effort.

Modern physiology has given us a very good understanding about the *control systems in the human body* which stabilize certain features of the internal environment. Within our bodies there are many control systems which, by detecting deviations or even by anticipating them, apply necessary correcting responses. Such systems control, for example, body temperature, osmolarity and the hydrogen ion concentration (pH) of the blood, glucose level & oxygen tension, blood pressure, cardiac output, respiration, pupillary diameter, and posture.

Control Systems

Biologists have borrowed many important concepts from engineers regarding control theory and systems analysis. For instance the feed-back or servo-mechanism has been used by engineers to automatically adjust the amount of steam delivered to the steam engine to keep a constant speed under a variable load. The human brain provides many such feed-back regulations. The control systems fortunately do not involve our conscious minds. We do not have to direct our fingers to stop touching something too hot—reflex nervous activity sees to that. Nor do we have to act consciously to digest food—the autonomic nervous system working together with the endocrine system (including gut hormones) organizes the secretion of various digestive juices as they are required to digest the food, and controls the motility of the stomach to deliver the right amounts of food at the right consistency to the intestines, and to adjust the motility of the intestines to achieve propulsion of food material over a wide absorptive surface to achieve absorption, and to expel waste matter.

The homeostasis of blood sugar is discussed in the chapter on "Chemistry of Life" under the heading of intermediate metabolism.

Hormones, Chemical Coordinators

Hormones act as chemical messengers and help to regulate activity, growth and repair of tissues in concert with the autonomic nervous system. Each hormone acts only on specific types of cells, those bearing the appropriate membrane receptor sites. These are "target cells" for the hormones. As hormones attach to receptor sites, they initiate a "switch on" reaction in the cell cytoplasm. For many hormones this reaction is the production of a second messenger, Cyclic AMP (adenosine monophosphate), which activates the cells' production lines. The activity in the blood stream of some hormones such as adrenaline, may last for only ten minutes. Others, including some sex hormones, have a longer duration. Hormones may be inactivated in the target cells or by the liver, and the breakdown products, when the hormone action is completed, are either excreted or re-used in the further manufacture of hormones.

In much the same way, for example, as the brain's control of muscle activity is constantly monitored and altered to suit the information received by the brain, so also is the activity of the endocrine glands constantly monitored and altered by nervous, hormonal, and chemical information being fed to them. Hormone production is controlled in many cases by a negative feed-back system, in which over-production of a hormone leads to a compensatory decrease in the subsequent production of the hormone until balance is restored.

Safeguarding against Blood Loss

In order that the blood shall continue to serve as a circulating medium, fulfilling the various functions of a common carrier of nutriment and waste, and assuring an optimum habitat for living elements, there must be *provision for holding it back* whenever there is a danger of escape. The serious bleeding which occurs in "bleeders" (when blood does not clot or clots too slowly) from so slight an operation as pulling a tooth for example, is proof of that.

The phenomenon of accelerated clot formation as more blood is lost from the body has long been recognized. In the latter part of the 18th Century Hewson noted that when an animal is bleeding to death, the latest blood which escapes clots more quickly than the earliest. In a typical experiment, the clotting time, as measured by an automatic device, averages about seven minutes. When about 13 per cent of the

estimated blood volume is withdrawn from the anaesthetised animal the clotting time is reduced to 2½ minutes, withdrawl of ten per cent more reduces the clotting time to about one minute which means 7 times faster clotting occurs. The Belgian physiologist Nolf showed that haemorrhage does not accelerate the clotting process after the *liver has been excluded* from the circulation. It is now appreciated that the liver manufactures several clotting factors and adds them to the circulating blood. It was shown by further experiments that the physiological method for hastening the clotting process requires the outpouring of the hormone adrenaline into the blood stream from the adrenal medulla.

Still another effect of the activation of the sympathetic system that is seen after haemorrhage is peripheral vasoconstriction. As 20 per cent of the estimated blood volume of an animal is withdrawn, the arterial blood pressure falls precipitously; in fifteen minutes, however, it is restored to normal, by increased peripheral vascular resistance; this has been shown experimentally by the prolonged perfusion time of a saline solution as the blood pressure falls, indicating an increased tone of the arterioles.

Maintenance of Blood Flow & Pressure

There is evidence that the extraordinarily sensitive brain and the continually active cardiac muscle have a volume of blood flowing through their vessels that is dependent directly on the general arterial pressure. If the pressure falls below a critical level, then organs may suffer irreparable damage. Therefore, even if there is a large haemorrhage, the vasoconstriction of the peripheral vessels, especially those of the skin, the fat depots and the skeletal muscles, aids to maintain blood pressure and blood flow to the brain and the heart. Disastrous injury begins only when in spite of the automatic adjustments, the corrective devices are taxed beyond their adaptive limits and the general arterial pressure then drops below the critical level.

In 1910 the French physiologist Hedon showed that when the blood pressure falls in the arteries of the head, there is general constriction of the blood vessel of the rest of the body. The Belgian physiologist Heyamans, showed that the low blood pressure in the head region acts as a stimulus to the nerve endings in the *carotid sinus,* a bulbous enlargement on the carotid artery where the branching occurs.

This emergency adjustment in the organism is followed by restoration of the blood volume from supplies of water and salt in tissue spaces, and from the functional service of *thirst.*

Thirst & Hunger

In Ayurveda there is emphasis on *not suppressing the natural urges of thirst and hunger.* Physiology has explained why this is so important not to suppress them. Thirst and hunger are of prime importance in making certain that the organism has the essential materials, water and food, for carrying out its functions. We all know that water and food are among the fundamental requirements of the organism, and that at all times both water and food are being spent. Non-volatile waste is constantly passing out through the kidneys. And volatile waste from the burning of food materials in the tissues is carried away by every breath. Acting as a vehicle for the discharge of this waste is water. Also water is continually being lost by evaporation from respiratory and skin surfaces.

Since water and food are being steadily lost from the body, the only way in which a constant supply can be maintained is by means of storage and gradual release. Water is stored in tissue spaces and in tissue cells. Food is stored in the fat depots (adipose tissue). When need arises these stored reserves are set free for use. The reserves themselves must be replenished.

Profuse sweating or excessive loss of fluids from the body as in the diarrhoea of cholera, or the abundant loss of water through the kidneys in diabetes, will provoke thirst to an intense degree. After severe haemorrhage thirst is tormenting. Thirst is the consequence of the drying of the mucous membrane of the mouth and pharynx, when the salivary glands fail to keep this region moist. On giving water the salivary secretion is promptly restored.

The Kidneys and the Internal Environment

The "milieu interior" or internal environment,the blood and plasma which the heart keeps in constant circulation throughout the body contains a multitude of compounds the concentrations of which are regulated with remarkable precision, and in this regulation the kidneys play a crucial role.

The importance of the kidneys in our vital economy can be appreciated in part from the fact that the two kidneys in man, although representing less than one half of one per cent of the body weight, receive about 20 per cent of the blood volume pumped by the heart. Each day more than 1700 litres of blood flow through the kidneys. Yet only about one thousandth of this huge flow is converted into urine. How does a kidney manufacture urine from blood?

William Harvey (1578-1657) discovered the circulation of blood but it was a young Italian of the 17th century named Marcello Malpighi

(1628 – 1684) who first fathomed how the blood conducts its traffic with the tissues. Malpighi was one of the earliest biologists to use the microscope, and he became the founder of microscopic anatomy. In 1661, four years after Harvey's death, Malpighi discovered the capillaries, watching the lungs and viscera of a living frog under a microscope. When he later came to examine the microscopic structure of the kidneys, Malpighi found some other highly interesting formations. Not long before, a 19-year old student of physics named Lorenzo Bellini had discovered minute hollow ducts in the cut surface of the kidney. He called them urinary canaliculi (little canals) and he observed that they coalesced into larger canals which in turn emptied into the hollow space, or pelvis of the kidney. Here then, was the route by which urine was excreted; it was clear that urine collecting in the kidney pelvis would drain by way of the ureter into the bladder. Malpighi now went on to show that Bellini's ducts drained a system composed of thousands of still smaller tubes in the kidneys. He had found that the kidney capillaries were bunched in innumerable little spherical tufts which he called corpuscles. Malpighi inferred, though he did not prove, that each of his capillary tufts was connected with one of the tiny tubes ("tubules").

Two hundred years later, in 1842 William Bowman, a young demonstrator of anatomy at King's College, London completed the anatomical picture. He showed that each Malpighian corpuscle is in effect formed by the intrusion of a tuft of capillaries into the end of a tubule, just as a fist would be enveloped if thrust into a large inflated rubber ball. The thin, greatly expanded walls of the tubule form a capsule surrounding the capillary tuft. The fluid in the space within this capsule (corresponding to the space within the indented ball) can drain freely into the tubules. Blood flows into the capillary tufts by one artery and flows out through another which breaks up into a second series of capillaries that is closely intertwined with the tubules.

We now know that each of the two kidneys in human beings, contains about one million such units, called nephrons. The spherical tuft of each unit known as a glomerulus (the diminutive of glomus, meaning ball) is located in the outer zone or cortex of the kidney. The tubule leading from it twists in a complicated manner around the glomerulus and then plunges in a more or less straight course into the interior of the kidney, where it makes a sharp hair-pin turn (loop of Henle) and runs back to the glomerulus again; there it winds about in a second series of twists and finally discharges into a urine-collecting duct. The average tubule in a human kidney is about an inch and a quarter long. If the two million nephrons in the two kidneys were put end to end, they would stretch for nearly 50 miles.

The typical mammalian tubule has a different cell structure in its various sections. The first segment, where it twists around the glomerulus, is composed of thick irregular cells possessing brush-like filaments on the inner side. The second segment, which plunges into the kidney to the loop of Henle, has a much smaller diameter and much thinner walls. The third segment, which leads into the collecting ducts, is made of somewhat flatter cells than the first, and lacks the "brush border".

The German physiologist, Carl Ludwig suggested the idea that the glomeruli are simply mechanical filters, beautifully contrived to permit the filtration from the blood of a cell-free and protein-free fluid. This filtrate passes down the tubules in large amounts, and as it does so a considerable part of its water is reabsorbed through the tubule walls into the blood stream. The residue, greatly reduced in volume and increased in concentration, passes into the kidney pelvis as the urine.

Ludwig's hypothesis was ably defended many years later by Arthur Cushney of University College, London, and it was validated by direct experimental evidence in 1921 by A. N. Richards and his coworkers at the University of Pennsylvania in U.S.A. The glomerulus of the living anaesthetized frog and the salamander can be visualised under the dissecting microscope. Keeping a glomerulus under direct observation an extremely fine glass pipette (micropipette) connected with an injection device and a manometer, was inserted by Richards into the glomerular capsular space. Injection of fluid into the space raised the pressure on the outside of the capillaries, and when the capillaries were seen to collapse, the pressure outside the capillaries was known to be slightly higher than the blood pressure within them. By this means blood pressure within the capillary tufts was found to be about 60 per cent of arterial blood pressure, a value far higher than the pressure in other capillaries of the body and more than enough to effect continuous ultra-filtration. Composition of the fluid from the capsular space, on analysis revealed the same concentration of total electrolytes, glucose, chloride, hydrogen ions, uric acid and so forth, as in an ultra filtrate of plasma.

The application of similar micropuncture methods, first to the frogs and salamander and more recently to those of rats, dogs and primates have revealed the tubular function, and its quantitative limits. Evidently filtration through the glomeruli does not account for all the substances found in the urine, nor indeed for the removal of all waste products from the blood. The tubules also play a part in this transfer of substances. The determination of precisely what substances the tubules

subtract from and add to the urine became possible when methods were found for measuring the rate of glomerular filtration (GFR). These measurements showed that the filtration rate in man averages about 125 millilitres per minute or about 180 litres per day, a figure which would have seemed scarcely credible to Ludwig or Cushney, the pioneer proponents of the filtration theory. Of the 180 litres of filtrate, 178.5 litres are reabsorbed into the blood through the tubules and only 1.5 litres are excreted as urine. Most of the salt and many other substances in the filtrate are reabsorbed. The excreted urine contains urea, creatinine and other products of protein metabolism; it also contains foreign susbtances that enter the body and the excess of sodium, potassium, phosphate, sulfate and other substances beyond the body's needs. These reabsorptive processes operate to recover valuable constituents from the glomerular filtrate which otherwise would be lost from the body, and it is partly by these processes that the *tubules maintain the constancy of the chemical composition of the plasma and body fluids.* For this active function (both reabsorption and excretion) the tubules need energy which must be made available to them within the cells by the metabolism of suitable fuel stuffs, and then put to work by suitable enzyme systems. These circumstances impose a limit on the rate at which any given substance can be reabsorbed. For instance the load of glucose imposed on the proximal tubular transfer mechanism is equal to the rate of glomerular filtration (ml/minute) times the concentration of glucose in the filtrate (mg/ml). If the load exceeds the maximal transfer capacity (Tm), that part of the load exceeding the Tm goes into the urine, as happens in diabetes mellitus. The Tm may be reduced in pregnancy, wherein one finds sugar in urine in the absence of an increased load.

E. K. Marshall and his coworkers at the Johns Hopkins University first proved the secretory function of renal tubules in 1924 by quantitative excretion studies with the dye phenol red. The list of substances excreted by the human tubules is rapidly expanding.

It is a matter of common knowledge that the rate of urine formation is quickly and substantially increased by the ingestion of water and is substantially reduced by dehydration. This regulation is achieved by the changes in water reabsorption in the tubules. Engineers have marvelled at the design of the renal tubule, especially the hair-pin loop system. An engineer suggested that the loop system might be a counter-current multiplier, long known in heat engineering as a device for multiplying small temperature difference to create a large

temperature difference. Following this suggestion, investigation soon established that the loop arrangement of the nephron is in fact, an osmotic counter-current multiplier which establishes a region of very high osmotic pressure at the tip of the loop. Since the collecting duct which delivers the final tubular urine to the pelvis of the kidney lies parallel to the loop and has its terminal orifice in the region of high osmotic pressure, the high osmotic pressure surrounding the collecting duct tends to draw water away from the final tubular urine. This conserves body water. A dehydrated man can excrete urine with osmolarity four times that of his plasma; but his kidney tubules are much inferior to the desert kangaroo rat who excretes urine with osmolarity 14 times that of plasma. The long loop of Henle in the renal tubule of the Kangaroo rat was a most important clue to the mechanism for concentration of urine.

In a classic series of studies at Cambridge University in England, E. B. Vernay and his colleagues have shown that an increase in osmotic pressure of blood causes an increase in the secretion of the anti-diuretic hormone in the blood.

Recent studies have shown that a rise in osmotic pressure of the internal environment is sensed by "Osmoreceptors" in the hypothalamic part of the brain; these cause the release of the anti-diuretic hormone (ADH) from the posterior pituitary gland. The hormone reaching the kidney via circulating blood, increases the permeability of the wall of the collecting duct, thereby increasing the reabsorption of water.

Sodium is the major ionic and osmotic constitutent of the extracellular fluid. Sodium is filtered in the glomerulus; since its concentration in this filtrate is 145 mEq per litre, about 26000 mEq or 600 gms. of sodium ions enter the renal tubules each day. Normally all but a few grams of filtered sodium is reabsorbed, most of it in the proximal tubule and the rest in the distal tubule and collecting duct. At those latter sites, reabsorption of sodium is coupled with secretion of hydrogen ions by the tubular cells. This is a major process by which acid-base status of the internal environment is adjusted, one sodium ion (Na^+) is reabsorbed for each hydrogen ion (H^+) secreted.

Since sodium is an important ion, there are fine regulatory mechanisms to govern its reabsorption through the renin-angiotensin-aldosterone axis; changes in the blood flow through the kidneys (for instance occurring due to congestive heart failure)

stimulate the kidney to secrete renin into the blood. Renin interacts with a protein in plasma thereby releasing angiotensin, the most powerful vasoconstrictor known. Angiotensin not only raises arterial pressure but stimulates the adrenal cortex to produce a hormone called aldosterone, which in turn stimulates tubular reabsorption of sodium. The modern diuretic drugs act by interfering with the tubular reabsorption of sodium at various levels.

Processing, Purification and Storage

The liver is a central chemical processing plant of staggering complexity. Weighing 1500 grams, it is the single largest gland in the body, and with more than five hundred functions so far identified it is easily the most versatile. Unlike other organs the liver is served by two distinct blood supplies. The hepatic artery supplies it with fresh oxygenated blood while the portal vein supply comes from the stomach and intestines carrying absorbed nutrients which the liver extracts, processes, and stores, and from other main abdominal organs, the spleen, the gall bladder and pancreas. The architecture of the liver is such that each hepatic parenchymal cell is washed by arterial blood bringing necessary oxygen, and portal blood, from which the liver cell removes nutrients. At the same time into this cascade of blood passing through the microscopic sinuses, the liver cells secrete glucose, proteins, vitamins, fats, and most of the other compounds required by the body. Bile, a solution of organic compounds in water, is also produced by the hepatic cells. The economy of the body is such that the waste products from the breakdown of old red blood cells are used as essential substances for the digestion and absorption of fats in the intestines. When haemoglobin is broken down in the liver, much of the iron that it contains is reutilised. Excess amino-acids from haemoglobin, or more generally from all the other proteins that are broken down, are either used by the versatile liver cells for building new proteins, or are further broken down to provide energy. Poisonous ammonia produced during this process is converted to urea, a non-toxic compound, and returned to the blood for transport to the kidneys, for excretion in the urine. Some amino-acids thus broken down can be converted in the liver into glucose which, with other excess carbohydrates, is stored in the liver cells as glycogen, ready for turning back into glucose should the level in the blood start to fall.

Fats are also removed from the portal blood by the liver cell where they are either stored, modified into more useful fats and returned to

the blood, or attached to specially made proteins to form compounds called lipoproteins, in which form most fats are transported to those organs that then use them as fuels.

The liver cell also acts as a storage bank for vitamins A, B, D, E and K. The size of those liver stores can be so enormous, that a well-nourished man can go for months without vitamin A and two to four years without vitamin B12, with no signs of deficiency.

The wide repertoire of hepatic enzymes enables the liver to act as a centre for protection against potential poisons. Because of this capacity, socially acceptable poisons like alcohol, and potentially toxic medicines like barbiturates can be consumed as custom or prescription requires. So-called poisons are compounds which damage the body cells before the liver has dealt with them. Interestingly the livers of strict carnivores, those who eat no food but other animals, have lost much of this detoxifying ability. They eat those animals whose livers have already filtered out potential poisons. Consequently compounds that may be harmless to human beings, if eaten by them can have severe and bizarre effects.

Sometimes a paradoxical situation arises. Tetraethyl lead for instance, a useful fuel additive for the petrol engine, is itself biologically inert. The mammalian liver contains enzyme systems which readily remove ethyl radicals to form triethyl lead ion, which can be excreted. Unfortunately, it is one of the most active inhibitors of oxidative phosphorylation that is known, and so interferes with brain metabolism. In order to get rid of the inert tetraethyl lead, the liver has produced an active poison for the brain.

Parathion, the well-known organo-phosphorus insecticide has practically no action against the enzyme cholinesterase, but both insects and mammals have enzyme systems which convert the P = S bonds to P = O and the resultant paraxon is one of the most active inhibitors of cholinesterase and appreciably more soluble than parathion.

The mammalian liver has enzyme systems which carry out N-demethylation, a useful reaction. If however, the inert material dimethyl nitrosamine is introduced N – demethylation results in the formation of a very unstable mono-methyl nitrosamine which in turn decomposes to liberate *diazomethane* which is extremely reactive, and if liberated inside the liver cells, can either kill them or in small doses is eventually carcinogenic.

Hence the wisdom of the human mind consists in not introducing

into his ecosystem such compounds which his body's wisdom cannot tackle effectively.

Immunity or "Vyadhikshamatva"

Ayurveda has propounded the concept of immunity as *"Vyadhi kshamatva"*. Although Louis Pasteur (1822-1895) established the "germ theory" of the infectious diseases, he was well aware of the effects of the environmental factors on the functioning of the living organisms, although he did not have time to investigate them experimentally. He discovered the *"seed"* but he also paid attention to the *"soil"* or the terrain by which he meant the internal and external environment of the host. In his study of the diseases of silk worms, which led to the germ theory, Pasteur recognized that these diseases resulted from a *complex interaction among host, germ and environment*. He wrote: "If I were to undertake new studies on the silk worm diseases, *I would direct my efforts to the environmental conditions that increase their vigour and resistance.*" Pasteur's view of human diseases showed the same ecological awareness. He pointed out that bacteria cause damage only when the body resistance is weakened. "How often does it occur that the condition of the patient, his weakness, his mental state, form but an insufficient barrier against the invasion of the infinitely small ones." Critics of "germ theory" should do well to ponder over these words of Pasteur.

Natural Defenses of the Body

The human body is a vulnerable organism living in an essentially hostile environment in which disease-causing bacteria, viruses, fungi and parasites abound. Without an efficient defense system we would soon succumb to their assault. However, not all micro-organisms are undesirable. Indeed many are permanent residents of our bodies. The bacteria which live on the skin, for example, are like a mercenary army assisting in the defense of the body. Their very density leaves no foothold for less desirable colonists, and the compounds they produce are inhibitory to other micro-organisms. The same is true about bacteria in the human large intestine.

The skin is the first major barrier to assault by unwelcome invaders. The skin, the body's largest organ, is tough, flexible, self-repairing, waterproof and almost all-enveloping except at the body's orifices where it is modified to form mucous membranes; the mucus they secrete is thick, slow moving and an effective trap for bacteria. In the

airways ciliated cells push mucus containing inhaled dust particles and bacteria towards the throat so that they can be coughed out or swallowed. In the eyes the tears havẹ washing properties. Hairs in the nose and ears and the cerumen in the ears have great trapping ability. In addition sneezing and coughing are additional protective reflexes. The acid in the stomach and acid pH of the vagina are detrimental to bacteria. Vomiting and diarrhoea are other protective reflexes aimed at getting rid of ingested noxious material.

If the foreign invaders succeed in penetrating the skin or mucous membranes, there is another line of defense, the white blood cells which can engulf and deactivate many foreign particles. The circulating white blood cells as well as macrophages resident in the liver, spleen, lungs, lymph nodes and bone marrow have crucial phagocytic function. In addition natural killer (NK) cells attack and eliminate any abnormal cells they encounter, like cancer cells.

Immunological Responses

The living organism has the capacity to recognize foreign agents and to respond specifically through specific cells (immunocytes) or specific antibodies (immunoglobulins). A remarkable feature of the immune response is its *memory*. Once the body recognizes a foreign agent (antigen) and produces specific immune response against it, the information is stored in "memory cells"; next time the antigen enters the body the response is prompt, more aggressive and more efficient than the first encounter. This is the basis of active immunisation, and for instance, the "booster dose" of tetanus toxide immediately after an injury.

There are two different types of lymphocytes, T-cells and B-cells. They are identical in appearance but function in different ways when exposed to an antigen. The thymus gland plays a crucial role in training the T-cells, making them immunologically competent and maintaining the immuno-competence. Such competent T-cells lodge themselves in the lymphoid tissue. When a T-cell comes into contact with an antigen, it divides rapidly and forms many daughter cells, all with the identical property of being able to attach themselves to that particular antigen. If the antigen is a cancer cell, it is attacked and destroyed by a type of T-cell called *killer T Cell*. Some T-cells act as *helper cells* to another class of cells, the B-cells to produce antibodies. B-cells do not pass through the thymus gland before they settle in the lymphoid tissue, but are believed to be formed in the gut lymphoid

tissue. The B-cells are the sources of circulating antibodies, specifically structured proteins called immunoglobulins (Ig). Various types of immunoglobulins seem to be specially suited for various kinds of antigens. For instance IgM is more efficient in trapping and destroying large bacilli like salmonella, IgG is efficient in trapping pneumococci. One special type of Ig, called secretory Ig A is secreted in the alimentary and respiratory tracts and provides a protective mantle against invading microbes including viruses. The breast milk provides ready-made IgG and secretory IgA for the infant for six months until its own immune system matures and takes over. This is one important reason to encourage breast feeding, apart from the nutritional aspects.

Antibodies can react in several ways when they come into contact with antigens. The antibody can attach itself to the antigen and neutralize it by covering on the membrane the chemical groups which have a specifically toxic effect. This combined particle is then ingested by macrophages. Antibodies are also capable of clumping (agglutinating) or linking together many molecules of the antigens. This creates a mass which, again, macrophages are able to destroy.

A protein which constantly circulates in the blood stream, known as *complement,* is able to fix itself at the site of antigen-antibody combination. It then activates a series of enzymatic steps which eventually penetrate the cell membrane of the invading agent and cause it to rupture. Here again the macrophages and neutrophil white blood cells act in concert to "finish the dirty job".

One of the most remarkable aspects of the immune system is its ability to recognize *self-antigens* (antigens on own normal body tissues) and not attack them. The mechanism of immunologic tolerance is being understood better now and is mediated by a special type of T-cells called *suppressor T Cells* which, again, are trained and regulated by the thymus.

Sometimes the wisdom of the body falters and immunological attack is now directed against *own* tissues. This leads to a group of diseases called "auto-immune" diseases. This is not the only way that the immune system can go wrong. Hypersensitivity reactions, often described as allergies, are caused when such normally harmless substances as dust, pollen or cat's fur, trigger an immune response with resulting uncomfortable symptoms such as sneezing, itching and over-production of mucus and tears.

Inflammation and Repair

The human body has a remarkable capacity to repair injuries and reconstitute defects. This response to injury has two themes, inflammation and repair, but they are so closely intertwined as to comprise a single story. Inflammation may be defined as the response of the body to tissue injury involving neurologic, vascular, humoral and cellular reactions within the site of injury. This response serves to destroy, dilute or wall off the injurious agent and the tissue cells it may have destroyed. The inflammatory response, in turn sets into motion a complex series of events which, as far as possible, heal and reconstitute the damaged tissue. Repair begins during the active phase of inflammation but reaches completion only after the injurious influence has been neutralized. Destroyed cells and tissues are replaced by normal cells, some times by regrowth of the native parenchymal cells, but more often by filling the defect with less specialised fibroblastic scar-forming cells. When the inflammatory reaction is prompt and effective, the need for repair is minimised and may lead to little or no scarring.

Vital as these responses are to the maintenance of health, both inflammation and repair can be potentially harmful. Inflammatory reactions underlie the genesis of several forms of serious kidney disease, crippling rheumatoid arthritis and life-threatening hyper-sensitivity reactions. Reparative efforts may lead to disfiguring scars, fibrous bands which limit the mobility of joints, as well as masses of scar tissue that hamper the function of organs. Fortunately, such unwanted outcomes are exceptions and not the rule.

The basic character of the immediate inflammatory response is almost always the same, regardless of the location or nature of the injurious agent. The injurious agent may be living agents like bacteria or non-living agents such as extremes of heat and cold, radiant energy, electrical or chemical injury, or simple mechanical trauma. Moreover, the necrotic products released serve as inflammatory stimuli.

Depending upon the severity of the injury and the adequacy of the host defence, the inflammation may remain localised to its site of origin and evoke no systematic reactions, or may call into play systemic responses. The local clinical signs of inflammation have been classically described by Celsus as *calor* (heat), *rubor* (redness), *tumor* (swelling and edema), *dolor* (pain), to which *functio leaesa* (loss of function) can be added as the fifth sign.

Pus is an inflammatory exudate rich in proteins, which contains viable white blood cells as well as cell debris derived from necrotic immigrant leucocytes and native parenchymal cells.

Chemical mediators of the inflammatory response have been identified. These can be divided into five groups.

1. Amines – Histamine, serotonin (5-Hydroxy tryptamine)
2. Kinins – Bradykinin, Lysyl bradykinin
3. Protein and tissue extracts – globulin permeability factor, proteases etc.
4. Miscellaneous group – SRS (Slow reacting substance), Lysolecithin, Esterases of Complement.
5. Prostaglandins – Probably these are the final mediators of pain and inflammation. Histamine, bradykinin, and polymorph leucocytes during phagocytosis, release PGE. Vasodilatation caused by PGE is not abolished by atropine, propranolol, methysergide or antihistaminics, known antagonists of other possible mediators of inflammation.

Repair Process

Repair comprises the replacement of dead or damaged cells by healthy cells. These new cells may be derived from either the parenchyma or the connective tissue stroma of the injured tissue. Parenchymal regeneration can completely reconstitute the defect, leaving no residual trace of prior injury. However, in the human body such perfect reconstitution of the native architecture occurs only under very limited conditions. The advantages that man may have gained in the evolutionary process have been accompanied by loss of capacity to regenerate severely damaged organs. Because of these limitations repair of tissue injury usually takes the form of connective tissue scarring. Such repair may fill defects and more or less restore morphological continuity, but it usually replaces specialised functioning cells with non-functioning connective tissue. Such scarring depletes the functional reserve of an organ or tissue.

The cells of the body can be divided into three groups based on their regenerative capacity; labile, stable and permanent cells. Labile cells continue to proliferate throughout life, such as the epithelial surfaces of the body, skin, mucosa, uterine lining etc. The red and white blood cells and platelets are in the same category.

Stable cells include the liver, pancreas, endocrine glands, kidney tubular cells, and the mesenchymal derivatives such as fibroblasts, osteoblasts and chondroblasts. It is postulated that injury to stable cells derepresses the genetic programmes which repress mitotic processes in the quiescent cells.

Permanent cells like the nerve cells are highly specialized and cannot undergo mitotic division in post-natal life, presumably because the genetic programmes involved in their division are irreversibly and irrevocably repressed. Severe injury to such cells inevitably implies loss of specialised function. Perfect repair can occur only in tissues made up of labile and stable cells.

Most of existing evidence suggests that the trigger for cell proliferation consists of some local loss of inhibitory influences at the cell level, which thus permits affected cells to proliferate. Stimulatory factors, so called wound-hormones may also stimulate replication. The concept of *"chalone"* proposes that such tissue produces and contains its own specific inhibitors. With injury, chalones diffuse out of the cells, permitting regeneration. In tissue cultures contact inhibition is observed in which cells are inhibited from mitotic division by the interchange of signals or substances at their points of contact.

Nutrition has profound effect upon the inflammatory-reparative response, particularly in the healing of wounds. Adequate blood supply in an area of injury is obviously important. Foreign bodies and unabsorbable sutures constitute impediments to healing.

The Margin of Safety

In 1907, Meltzer discussed the question – How are our bodies built? Is barely enough provision made for keeping us intact? Or is there allowance for contingencies? Have safety factors been introduced on which we may count in times of stress?

Modern physiology has answered many of these questions. Stores of carbohydrate, protein and fat are set aside in the body for use when supplies from outside are not available. Although the blood sugar is usually kept up to 90 to 100 mg. per dl, it can fall to 70 to 65 and some times lower, without producing disagreeable symptoms. Of course, levels below 50 make for serious trouble. Hence the margin of safety in blood sugar would be about 100.

Normal serum calcium is about 10 mg/dl. Convulsions occur when the concentration is reduced to 6 mg/dl; or when it rises above 14 mg/dl again it is life-threatening.

Normal serum potassium is 3 – 4 mEq/litre. Below 2.5 and above 6.5 are dangerous levels.

In the cardiovascular system there is a large factor of safety. Although the normal systolic blood pressure is 110 – 120 mm Hg, it

may drop to 70 before reaching the critical level at which the bloodflow to the tissues is compromised. The vasomotor apparatus is organized for security. A series of devices assure the maintenance of adequate bloodflow to the heart and brain in particular, some times at the cost of other organs, during an emergency.

The normal heart is capable of increasing its pump function to 5 – 6 times normal. The left ventricle can continue to function as an efficient pump even when more than half its muscle mass is dead. An efficient circulation can be maintained when the walls of the right ventricle are nearly completely destroyed or when blood is made to bypass the right ventricle. Obviously, the heart is equipped with large factors of safety to meet the strains of everyday life. This applies also to heart valves. Doctors have long been aware that patients can maintain a good circulation despite serious leaks in the heart valves. The physiological factor of safety is the mechanism known as Starling's law; the more a cardiac muscle is stretched, the more vigorously it responds, of course within limits. In one outstanding respect the heart has no great margin of safety, namely its oxygen supply. The amount of blood supply is therefore all important to the heart particularly when activity raises its oxygen demand.

The respiratory function has also got lot of reserves. During exercise, the demand for extra oxygen is met by a six-fold increase of pulmonary ventilation. A person can get along with one lung if the other one is collapsed or removed by surgery. Kidney transplant by living donors is possible only because a healthy person can get along with only one kidney.

The adrenal cortex is essential for life, but if only 1/10 of the adrenal tissue is left behind following surgery the life of the patient can get along. 4/5 of the thyroid can be removed, without causing thyroid deficiency.

The liver has tremendous regenerative powers. The pancreas is important for both its exocrine and endocrine secretions but only 1/5 is necessary to furnish the insulin requirement of the body.

Nature Cure and Naturopathy

The concept of "The *vis medicatrix naturae*" or the healing force of Nature, held by Hippocrates, indicates the recognition of the fact that processes of repair after injury, and of restoration to health after disease, go on all the time quite independent of any treatment which a

physician may give. It is indeed a thought worth pondering that throughout the history of medicine and mankind, people have claimed credit for their treatment which really belongs to the *natural process of healing*. It is only in the 1940's that medical men began applying critical scientific criteria for evaluation of therapy (see chapter 3: Scientific Evaluation of Therapy). If the body can largely care for itself, what is the need and use of a physician?

The appeal for Nature Cure and Naturopathy has been increasing in recent years especially in the context of increasing mistrust and dissatisfaction with modern medicine and its potential for creating iatrogenic illness. To the extent that this approach stresses that health and illness are mediated by the person's own behaviour, and therefore a person should be responsible to maintain his own health, it does not conflict with the institution of scientific modern medicine. The well-trained physician in fact realizes better than the layman that many of the remarkable capacities of the organism for self-adjustment require *time*—all of the processes of repair belong to that class—and that they can play an important role in restoring the organism to efficiency only if they are given the chance which time provides. The wise physician therefore helps to create conditions which permit healing. He allows only such activities as are necessary until lost or injured parts have been rebuilt, strengthened or compensated for. The physician plays his part in making effective the self-regulating adjustments of the body that have been disordered, or that are in need of reinforcement.

When a person gets a fracture, the physician knows that nature is going to provide the repair process. The physician assists nature by providing the optimum conditions for repair (such as proper alignment of the broken ends and immobilisation by plaster). By suturing a wound, the surgeon is facilitating and accelerating the natural process of repair.

When a person gets burnt, again nature is going to provide the repair process. The physician helps by protecting the vulnerable skin from super-added infection, by providing replacement of fluids and electrolytes lost through the burn, and finally to repair and reconstruct by plastic surgery those areas which have been totally destroyed and scarred.

What is of crucial importance, the well-trained physician is acquainted with the *limitations* of the self-regulatory and self-repair processes of nature. His intervention is again to assist nature to restore

normalcy. Thus, surgical relief of obstruction, stoppage of bleeding, replacement of blood, plasma, or saline-glucose intravenously, constitute life-saving interventions to assist nature when its adaptive processes are overwhelmed. What is not appreciated by many lay enthusiasts of nature cure and naturopathy, is that without those interventions the patient may have no chance of survival. Some of the most spectacular triumphs of modern medicine have been in the nature of such interventions which make all the difference between life and death. As a medical man, I had presumed this to be common knowledge, until I had an interesting encounter in 1963.

Refusal to take the "Poison" Chloramphenicol

While I was Professor of Medicine at the Nagpur Medical College and Hospital, I was called upon to go to Paunar Ashram to treat Acharya Vinoba Bhave, who was suffering from fever. I made a diagnosis of typhoid fever with certain complications, and urged him to take the drug chloramphenicol immediately. The inmates of the Ashram and close followers of Acharya (which included a well-known industrialist) were scandalised by the suggestion. They said they would not tolerate the idea of a "poison" like chloramphenicol entering the body of such a pious man as the Acharya. I had to firmly tell them that my regard and respect for the Acharya were no less than theirs, and that the expected beneficial effects of chloramphenicol in his particular situation were overwhelmingly greater than the possible harmful effects, and that in the absence of that particular drug therapy there was a high probability of fatal complications. The response to this was a statement that Vinobaji was a *"divya purusha"* (divine man), and that he would survive the complication like bleeding or perforation. I had to remind them that Lord Krishna was a *"divya purusha"* but when he was hit by the arrow of a hunter, the physical laws of nature asserted themselves, hence Vinoba's intestines would probably follow the same laws. The rationalist in Vinobaji got the message straightaway and he took the drug and experienced for himself the dramatic change of his condition in the next three days. When I saw him next time, a few months later for some other complaint, he told me that he got several letters of protest from his followers and admirers for not taking "Nature Cure". I told him that he did get cured by Nature, I only assisted nature at an appropriate time.

Myths and Fancies about Nature Cure

The "natural approach" to treatment has in recent years touched a

very sensitive area, that of treatment of cancer. Modern medicine is quite honest about the limitations of current modalities of cancer therapy, and the researcher's failure to cure cancer has drawn a large number of people to alternative remedies. There are at least a dozen national organizations in U.S.A., such as the Committee for Freedom of Choice in Cancer Therapy, The National Health Federation, The Cancer Control Society, and the International Association of Cancer Victims and Friends, which have hundreds of local chapters, publish regular periodicals, hold symposia and meetings and offer information about practitioners and counsellors in every state. The emphasis is on *natural cure* through "purification" through dietary regimens, "detoxification" and "internal cleansing" and "mind control". Often these treatment programmes stem from variant notions of human physiology and cellular pathology. For instance: "when oxidation is blocked, fermentation takes place in the cells and this is the cause of cancer". Another statement runs thus: "Over-indulgence in proteins and body's inability to properly utilise them, is one of the main causes of cancer". The Boston-based Hippocrates Health Institute claims that "no disease can exist when the blood is 'cleaned' and when the cells are 'rebuilt'". "Constipation is the greatest crime against health and the cause of cancer in some instances". So also, "improper diet and inadequate elimination of waste are pathological, hence the need to cleanse and purify the body through special (usually meatless) diets, internal irrigation and development of appropriate spiritual attitude". They stress the importance of avoiding unnatural and harmful treatments, such as surgery, chemotherapy and radiation therapy.

It is my fear that the humility of modern science in relation to cancer cure is being misused by gullible ignorance which is masquerading as pseudo-science. Arrogance of ignorance can be more devastating than the arrogance of expertise. Modern physiology knows today more about nutrition and health, and the role of digestion and absorption of nutrients and the role of toxic chemicals, than at any time in history. To bring into today's vocabulary such catch-phrases as "living foods" and "internal purification" and "cleansing the system" is a disservice to both science and society. It is the requirement of science to demand verifiable data, and the onus of providing it is on those who make such curative claims. The hope that such claimants will willingly accept the rigours of the scientific method is remote indeed.

Chapter 12

BODY AND MIND

Introduction

Charaka states: "The body and that which is called the mind are both considered to be abodes of disease, likewise of well-being. The cause of well-being is their harmonious or concordant interaction".

"*Vata, pitta* and *kapha* are said to be the complex of pathogenetic factors in the body; passion and delusion are considered to be the complex of pathogenic factors of the mind".

"The former type of morbidity is quieted by medication, divine and physical, and the latter by spiritual knowledge, philosophy, fortitude, remembrance and concentration".

Since every patient has a body and mind, any illness has mental aspects. Several decades ago, psychosomatic medicine began as a scientific discipline concerned specifically with the study of the relationship between the biological and the psychological aspects of health and disease. In the words of Rene Dubos, "whatever its precipitating cause and its manifestations, almost every disease involves both body and mind, and these two aspects are so interrelated that they cannot be separated one from the other".

Effects of Emotions on Body Functions

Folk language is full of colloquialisms expressing the appreciation of the connection between body and mind. We see "red with rage", or may become "blind with rage", or be struck "dumb with horror". Love is blind, and one may be able to speak to his loved one with a stutter or a stammer. The heart is traditionally the seat of emotions so that one may suffer from "heart ache" or be "heart broken". Fear may make the heart "come up in the mouth" or feel as though it is "sinking into the boots". One may feel "paralysed" by fear. Emotions are

commonly expressed through the skin: the maiden may blush with embarrassment or shame, she may flush with indignation. The skin also reacts to fear by excessive perspiration or production of goose pimples. Fear may make the flesh creep. Something, or some one may be said to "get under one's skin", or one may be "itching to do some particular thing". Other emotional disturbances may make one "go weak at the knees", "limp as a rag", or cause "the teeth to chatter", under an ordeal one may "grit one's teeth". Fear makes the mouth go dry; disgust or fear makes one sick. One cannot "stomach or swallow" a situation; one feels "a lump in the throat" or gullet, or feel a "load on the chest" or "knotted-up" inside. Relief is commonly expressed as "getting something off the chest".

Certainly there is nothing new in the recognition of the importance of body-mind unity in medicine as seen in the writings of Charaka and Sushruta.

John Hunter (1728 – 1793) had personal experience of the effects of mind on body, and had prophetically said that his life was in the hands of any rascal who chose to make him angry, since he had noted how his attacks of angina pectoris were brought about whenever his mind was agitated.

In 1884, William James, a Harvard psychologist suggested that certain environmental stimuli directly evoked responses from the body and that these visceral responses, from the internal organs including the heart, stomach, lungs, intestines, affect the mind to produce an emotional feeling. James summarised his entire theory in the statement, "we are afraid because we run, we do not run because we are afraid."

At about the same time, a Danish scientist, Carl Lange, produced a similar idea about the development of emotion. The two theories bound together and known as the James – Lange theory, proved to be a landmark in understanding emotion. Almost immediately however, the theory became the target of deep and strong criticism. The chief critic was Walter Cannon, who held that emotion is a state of heightened arousal and is part of an activation system. He believed that the activation continuum extends from sleep to panic. Together with P. Bard, Cannon produced an activation theory which contends that emotions serve as a part of an emergency system for activating the body. The Cannon–Bard theory was therefore in direct opposition to the James–Lange theory. According to the Cannon–Bard theory, the

seat of emotion was in the brain itself, specifically the thalamus. Outside stimulation was received by the thalamus, which in turn sent impulses to both the cerebral cortex and the viscera, in this way preparing the body for action. Emotion, they believed, resulted from the new heightened state of arousal.

Modern research has now shown that both these early theories are over-simplifications. Most modern theories emphasise the cognitive or thinking element in the formation of emotion. For example, people when told about a particular situation, tend to exhibit the correct emotion for the situation, whether or not their knowledge of the situation was accurate or first hand. This would indicate that all emotions tend to be "in the eye of the beholder".

To study emotions in depth they must be analysed, ordered and described. One of the major difficulties in doing a descriptive analysis of emotion is that emotions are usually relevant to the immediate context in which they occur, and even then they will vary with the intensity of feeling.

Feelings of pleasantness and unpleasantness, known as hedonic feelings, are regarded as the most fundamental emotional experiences. Included in the range of pleasantness are joy, love, laughter and contentment; while fear, grief, hate and resentment are unpleasant. Every emotion whether pleasant or unpleasant, is affected by the intensity of feeling and the amount of tension that the emotion generates.

To measure emotion, psychologists look at physiological changes in the body that are readily measurable. These normally include heart rate, blood pressure, breathing rate, and skin conductance. The electrical conductance of the skin, commonly called the galvanic skin response (GSR) offers an indication of emotional feeling, particularly of anxiety. Any feeling of emotion is normally accompanied by a change (rapid fall) in GSR. This is the principle upon which lie detectors work. Fast brain waves (EEG) are characteristic of an emotional state.

The Limbic System

Man may be said to have not one brain but three, which work together in reasonable harmony but differ from each other in structure, biochemistry and function. The upper brain stem—much of the reticular formation, the mid-brain and basal ganglia and hypothalamus—is the *primitive brain* whose task is largely the regulation

of stereotyped or instructive behaviour and of vital biological functions and rhythms. The *limbic system* was the second of the three to develop. The limbic system (as with all higher brain structures, there are two mirror-image systems one on each side of the brain) is nested deep in the temporal lobes. Each forms a ring around the brain stem and the basal ganglia. Various parts of the limbic sytem have intricate neural and biochemical connections among themselves and with both higher and lower areas of the brain. The details of these pathways are not yet precisely known but it is clear that they are concerned with memory and learning and emotional responses. Emotions are the conscious result of an interaction between the activities of the cerebral cortex, the limbic system and the visceral organs of the body via the hypothalamus, pituitary and autonomic nerves, which produce specific physical changes, thus explaining the relationship between body and mind.

The emotional function of the limbic system has been the object of much research in animals. The lower part of the limbic ring, fed by the amygdala seems to be largely concerned with feeding, fighting, fleeing and copulation. Electrical stimulation of these regions can cause emotion-based behaviour indistinguishable from that produced in the normal way – except for example that the enemy provoking the rage or flight is non-existent. Amygdalectomy will render dominant and aggressive animals docile.

In human experiments rage, agitation, anxiety, elation, excitement, colourful vision, deep thoughtfulness, sexual interest and relaxation have all been produced as a result of electrical stimulation of the amygdala, hippocumpus and septum.

Owing to the connections between the limbic system and the cortex, emotion is open to the influence of reason, and reason may similarly be affected by emotion. Disordered limbic function may be at the root of some mental diseases.

The limbic system contains most of the "reward" and "punishment" centres which enable us to assess the results of our actions and to learn whether or not it is desirable to repeat them. A fascinating region is the *"pleasure centre"*, stimulation of which causes quasi-orgasmic bliss or deep pleasurable relaxation. The limbic system still holds many mysteries but it may well hold the key to a fuller understanding of neurosis and mental illness. (For further discussion see chapter 13: "Understanding Mental Illness").

Psychosomatic Medicine

Dunbar in 1934, coined the adjective "psychosomatic" to describe the body-mind relationship. His book, "Emotions and bodily changes", published in 1935, contained 2358 references; this figure was doubled to 4717 in the fourth edition of the book published in 1954.

The American journal "Psychosomatic Medicine" was published in 1937. The 14th edition of Osler's "Principles and Practice of Medicine", edited by Christian in 1942, opened with the first chapter devoted to psychosomatic medicine. In the same year the Society for Psychosomatic Problems (later the Psychosomatic Society) was formed. A year later, Weiss and English in 1943 published their text book on "Psychosomatic Medicine" with its wealth of evidence to illustrate the psychosomatic concept as seen in clinical practice.

Balint wrote in 1957 a book entitled "The Doctor, his patient and the illness", in which he emphasised the need for a more comprehensive, deeper diagnosis of each patient than is normally thought necessary, an overall diagnosis which includes everything that the doctor knows and understands about the patient as a person. The patient has to be understood as a unique human being, and the emphasis (from the time of the Renaissance in Medicine) which had shifted to *illness-centred medicine* had to be brought back to *patient-centred medicine.* This approach is also emphasised in a book edited in 1972 by Hopkins, entitled "Patient-centred Medicine".

The Mechanism of Psychosomatic Disorders

The way in which emotional disturbances produce somatic symptoms may be sub-divided for sake of discussion into (1) the physiological mechanisms and (2) the clinical presentations.

Emotions exert their somatic effects largely through the autonomic nervous system. The central nervous system consists of two parts:

i) The cerebral or thinking part,
ii) The hypothalamic portion, which is responsible for vital functions not on a conscious level.

Under stress the body prepares itself for instant action as a protective mechanism, and this is effected through the autonomic nervous system as well as through the release of various hormones. Most ductless glands are controlled by the pituitary, and the pituitary is in turn controlled by the hypothalamus. Increased blood levels of ACTH can be demonstrated within two minutes of an emotional stimulus. Emotional

stimuli may also lead to alterations in the release of thyrotrophic and gonadotrophic hormones. In some people the automatic nervous system is more reactive than in others and in the twentieth century this is probably more of a handicap than an advantage. The sympathetic system was so called because it coordinated bodily functions but today it is more important as the pathway for translating emotional disharmony into visceral symptoms. Although much of the control of the autonomic nervous system is located in the hypothalamus it has been shown recently that it can be influenced from different regions of the cerebral cortex, especially the motor area, the orbital surface of the frontal lobe and the temporal lobe.

The visceral reactions of emotional stimuli are of two types.

1. *Sympathetic:* This is the part of the autonomic nervous system concerned with emergency situations in the external environment, *the preparation for fight or flight.* Fear is associated with the instinct to run and escape, the feelings of anger or aggression with the instinct to attack. The sympathetic nervous system, which adjusts the body to such stresses, therefore inhibits the metabolic processes of the body and increases the heart rate and blood pressure and mobilizes carbohydrate reserves. Its effects are mediated through (a) adrenaline, the body's emergency hormone, which is released from the adrenal medulla, and (b) noradrenaline, which is liberated at sympathetic nerve endings; although it comprises one-quarter of total catecholamine secretion of the adrenal medulla, it is largely concerned with the circulatory adjustments necessitated by changes of posture and exercise.

Adrenaline increases the heart rate, venous pressure and strength of cardiac contraction; it also diminishes the total peripheral resistance and augments the coronary blood flow. Blood flow through the skin and kidneys is dimished but that through skeletal muscle and the liver is increased. Adrenaline also enhances the irritability of the myocardium and predisposes towards cardiac arrhythmias. It inhibits movements of the stomach and intestine, which become relaxed. Carbohydrate utilization is enhanced and the blood sugar rises as a result of mobilization of liver glycogen. Adrenaline is primarily concerned with the metabolic adjustments to stress whilst noradrenaline is restricted to circulatory alterations. Noradrenaline has a powerful vasoconstrictor effect on all but the coronary blood vessels and so increases the systolic and diastolic blood pressures. It increases the strength of cardiac contraction, does not affect myocardial irritability and slows the heart rate. It is primarily released under conditions necessitating circulatory adjustments, such as exercise

or changes of posture. Adrenaline is released in response to emotional stimuli and pain.

2. *Parasympathetic:* This is concerned with the conservation and anabolic processes of the body. Hence there is stimulation of gastrointestinal and bronchial secretions, a storing of sugar in the liver; protective reflexes will also occur such as the contraction of the pupil against light and spasm of the bronchiolar muscles as a protection against irritant substances. Parasympathetic effects are mediated through the secretion of acetylcholine. If a person is given intravenous acetylcholine he experiences a feeling of warmth and flushing due to vasodilatation, and sweating due to cholinergic stimulation of the sweat glands. This is associated with nausea, vomiting and abdominal colic due to increased peristalsis and contraction of the intestines and stomach and is followed by loss of consciousness or a faint due to the fall in blood pressure. After regaining consciousness a feeling of profound weakness predominates as if months of ill-health had been suffered.

Effect of Organic Disease on the Emotions

Whilst many emotional diseases present with somatic symptoms, many organic diseases present emotional symptoms.

The effects of organic diseases on the emotions may be direct such as the psychiatric symptoms of enhanced sensitivity to catecholamines resulting from hyperthyroidism, or those due to virus infection on the limbic system. Alternatively, the effects of organic diseases on the emotions may be an indirect or personal reaction to the illness.

1. *Direct Effects.* The delirium of acute fever, the depression of influenza, infectious mononucleosis and the common cold, and the irritability of the convalescent, illustrate how organic infections may directly affect the limbic system and its control of mood. Cerebral vascular disease or tumour may present with emotional symptoms; the inability to cope with work when suffering from such organic disease may provide the stress necessary to provoke psychosomatic symptoms. Depression may occur secondary to anaemia, myxoedema, carcinoma or any chronic debilitating disorders. Postconcussional states may present with psychiatric symptoms, and disturbances of memory and delusions are characteristic features of the alcoholic psychosis described by Korsakoff. The euphoria of disseminated sclerosis, the obsessions which may follow encephalitis, the irritability associated with hypertension, the anxiety of thyrotoxicosis and the autonomic disturbances of the

menopause are reminders that psychiatric symptoms may be the presentation of organic diseases.

2. *Indirect Effects.* Organic disease may cause anxiety, and mental changes are likely to occur as secondary phenomena to any distressing illness. The recognition of disease by a patient leads to an intensely personal evaluation of the situation and this is affected by his previous experience of disease, his personality, his intelligence and his imagination. The stolid phlegmatic type will accept the situation and his resources will be directed to overcoming his disease. The anxious, fearful patient, who perhaps has had more than his fair share of pain and discomfort in the past, may disintegrate. Thus relaxed, contented patients recover from organic diseases more quickly than those who are anxious and fretful.

However, emotional disorders are common and an association with organic disease may be coincidental. Neurotic patients are just as likely to suffer organic illness as patients with a normal personality and so evidence of emotional disorder in a patient does not exclude the presence of organic disease. Furthermore, as organic disease may precipitate emotional illness the symptoms of which the patient complains, may be misleading. A patient may be obsessed with his heart and complain only on cardiac symptoms, whilst he is in fact dying of abdominal carcinoma.

Organ Responses to Emotion

Cardiovascular Responses

During rage, the clotting time of the blood is markedly shortened. During resentment, regret or anger, the pulse rate, blood pressure and cardiac output all increase. Anxiety causes an increased heart rate, oxygen consumption and cardiac output but lowers peripheral resistance. In patients with cardiac disease, anxiety and resentment have been shown to induce changes in the electrocardiogram, particularly alterations in amplitude and direction of the T wave. Emotional effects on bodily function are not confined to man alone. Myocardial infarction occurs in Kenya baboons subjected to the emotional stress of being trapped, and this takes place in the absence of vascular diseases. Myocardial infarction in this situation is occurring on a functional basis, presumably through coronary artery spasm secondary to rage.

The psychogenic faint, initiated by such emotional factors as fear, is associated with parasympathetic overactivity, resulting in vasodilatation

of blood vessels of the splanchnic area with a consequent fall in circulating blood volume and loss of consciousness.

Gastro-intestinal Responses

In patients presenting with gastro-intestinal symptoms, the underlying illness is more commonly due to a functional disorder than to organic disease. The secretion of gastric juice is influenced by anger, joy and anxiety. Secretion of saliva, intestinal juices and bile are also affected. Direct observations of the human colon through fistulae and colostomy openings and on the gastric mucosa through gastrostomy have shown that fear, anxiety and pain cause an increase in peristalsis with reddening and swelling of the mucous membrane, whilst depression causes reduced motility and pallor of the mucous membrane. Psychosomatic symptoms may be the result of disorders of secretory function such as salivation, dry mouth, hyperchlorhydria, functional hyperinsulinism and mucous colitis or, alternatively, they may be due to disorders of motor function such as oesophageal spasm, gastric hypermotility, spastic colon, biliary dyskinesia, constipation and diarrhoea. Whether the functional disturbance of hyperchlorhydria resulting from psychosomatic disorders can cause a peptic ulcer is uncertain. Peptic ulcer can still occur after the vagus and splanchnic nerves have been cut so that it seems more probable that emotional stimuli are only predisposing factors rather than a basic cause.

Skin Responses

The skin plays an important part in the regulation of body temperature by sweating, and its functions are controlled by the autonomic nervous system. Vasoconstriction, vasodilatation, pilomotor activity and sweating are the four common physiological processes of the skin and are all largely controlled by the automatic nervous system. Thermal and emotional sweating differ. Thermal sweating is most evident on the forehead, neck and front and back of the trunk and is controlled by the temperature centre in the hypothalamus. Emotional sweating is most evident on the palms and soles and in the axilla. Patients with emotional cold sweating do not suffer any increase of palmar sweating when exposed to heat, though other body surfaces respond to heat by increased sweating.

Itching can be purely psychogenic, independent of specific excitement of peripheral end-organs. The itch threshold is lowered by emotional experience and this can be demonstrated by intradermal histamine before and after emotional stress.

An increased tone of the sympathetic nervous system in tense patients is reflected by vasoconstriction of the blood vessels to the skin. Sedation of the anxious patient causes a reduction of the excessive sympathetic nervous activity and a return to normal of the skin circulation.

Respiratory System Responses

The influence of emotion on respiratory function is well recognized by the everyday expression "it took my breath away". The efferent innervation of the respiratory tract, which includes the nasal mucosa, consists of sympathetic and parasympathetic nerves. Parasympathetic nerves exert a constrictor effect on the smooth muscle of the respiratory tract and the sympathetic nerves have a relaxing influence. If parasympathetic stimulation to the lungs is excessive, mucous cells over-secrete and vasodilatation of blood vessels occurs. This produces swelling of the bronchial mucosa and congestion of airways. In addition, the smooth muscle of the bronchiolar walls constricts. The effects of emotional factors are mediated through the parasympathetic nervous system; and acetylcholine, like histamine, can produce all the symptoms and tissue changes of asthma. The nasal mucosa may also be involved. Thus, in the nose parasympathetic overactivity produces a thickened mucous membrane with watery secretion typical of vasomotor rhinitis. The emotional factors most likely to precipitate these parasympathetic effects are the feelings of humiliation and resentment. The factors determining whether increased parasympathetic activity will precipitate vasomotor rhinitis or bronchial asthma are largely determined by heredity.

Although hay fever is regarded as the prototype of allergic disorders, emotional factors play a precipitating role in many cases and in the majority of patients, in whom rhinitis becomes perennial, emotional factors have an important role. It has been shown experimentally that when the nasal mucosa is congested as a result of emotional stress, exposure to a dose of pollen, which does not normally cause symptoms, will give rise to hay fever. Thus allergic responses are potentiated by emotional tension both clinically and experimentally. Respiratory infection also causes the mucous cells to oversecrete and blood vessels to dilate and this will prolong or intensify allergic asthmatic attacks.

Asthma is usually a disorder of multiple causation in which infection, allergy and emotional factors all play a part. Infection is the most important factor precipitating disease and is responsible for over 50 per cent of cases. Allergy accounts for 25 per cent. and emotional factors

are probably contributory in 25 per cent. It is, however, important to realize that the main cause of asthma at the onset of the disease does not necessarily remain the dominant aetiological factor throughout the course of the illness. Thus a child who develops asthma as a result of infection may, in later years, have attacks secondary to emotional tension. It is worth stressing again that in most psychosomatic disorders the aetiological factors are several and the contribution of the emotional component is of variable relevance.

The Biochemistry of Anxiety

Anxiety neurosis is a common condition in which patients have a variety of complaints—palpitation, easy tiring, breathlessness, nervousness, chest pain, sighing, dizziness and faintness, apprehensiveness, headache, parasthesias, weakness, tremors, insomnia, sweating, anorexia, vomiting and diarrhoea, frequency of micturition, fear of death etc.

Paul D. White and his colleagues at Harvard demonstrated the familial nature of anxiety. In a random sampling of the general population the incidence of the disorder was 4.7% but among relatives of patients it was several times higher. With one parent affected 48.6% of the children suffered from anxiety neurosis; with two parents affected 61.9% of the children suffered. With neither parent affected but with one child suffering from anxiety neurosis 27.9% of the other children in the family were affected whereas the incidence in children in the general population was 4%. Is it *genetic* or due to common *environment?* Probably both.

Some of the symptoms of anxiety neurosis resemble these produced by physical exertion, and indeed most patients report that physical activity can bring on or intensify their symptoms. The rise in lactic acid (or lactate, to speak of the ionic form of the substance) is interesting. Cohen and White found that the lactate level was significantly higher in the patients before and after exercise, than in normal controls.

It occurred to Dr. Pitts to experiment with lactate infusions that were sufficient to raise the venous lactate level to between 12 – 15 millimols per litre (a range that is normally attained with only maximum muscle exertion) or after the administration of adrenaline. A 20-minute infusion *did* in fact produce anxiety attacks. 13/14 patients and 2/10 controls developed acute anxiety attacks during lactate infusion. With lactate plus calcium only a small minority developed symptoms of parasthesia compared to the high number in lactate infusion

alone. Patients had no symptoms when infused with glucose solution, as a control.

Adrenaline steps up lactic acid production by acting on metabolic receptor sites on the cell surface to activate the cell's glycolytic enzyme system. Propranolol (B-adrenergic blocking agent) blocks these sites. Double blind trials with propranolol and placebo have shown the former to eliminate anxiety symptoms.

In a recent report members of the New York Philharmonic Orchestra successfully employed propranolol to help overcome the stage fright which is so common among performing artistes. Reducing the adrenergic-mediated activity by drugs or by meditation is a rational approach for the management of anxiety neurosis.

Management of Psychosomatic Disorders

The diagnosis of emotional disease should be made on its own merit and not by the mere exclusion of an organic cause for a patient's symptoms. Certain somatic symptoms strongly suggest, but do not prove, an emotional origin and these include weeping, trembling, impotence, frigidity, palpitations, sighing respirations, difficulty in filling the lungs, pressure feelings on the head and complete physical exhaustion.

For effective management of patients with psychosomatic disease it is important to know how much of the illness is due to organic disease, how much is due to personality defects, and how much to stress. It is therefore necessary to investigate the mental as well as the physical state and the total life situation. A full clinical examination is necessary to exclude organic disease. Not only may organic disease precipitate emotional disorder, in which case the symptoms are likely to be misleading, but organic and emotional disease may coexist in the same patient.

Having understood the role of psychological influences in the development of illness, the important question is *how to alter* these influences. The recent discovery of *biofeed-back* phenomenon indicates that a wide range of physical processes can be influenced by a person's mental efforts. It is part of health education to make patients aware that they have participated consciously or unconsciously in the origin and development of their illness, and hence will also be able to participate in the healing process. Ayurveda emphasises the patient's participation in the causation of his own illness by the term *"Pradnyaparadha"* or "volitional transgression" of the rules of healthy living.

The idea is not to put blame or guilt in the mind of the patient for being unwell, but to explain to him that he made certain choices to expose himself to those stresses in certain ways. These choices might have been made deliberately or unknowingly, and would have been conditioned by his or her personality, various external constraints and by social and cultural conditioning. His participation in therapy is by adopting the necessary changes in mental attitudes and life style.

A positive mental attitude combined with specific stress-reduction techniques will have a strong positive impact on the healing process. In the discussion on "Placebo effect" (chapter 3 on "Scientific Evaluation of Therapy") I have discussed at length the healing power of the *patient's positive expectations,* supported by interaction with the therapist. On the other hand negative attitudes of the patient, the doctor, or the family may produce an "inverse placebo effect".

"Laughter, the Best Medicine"

The Bible tells us that a merry heart works like a doctor. Exactly what physiological changes in body and mind are produced by cheerfulness, mirth and laughter are not studied but one can imagine that the effects would be just the opposite of those of fear, rage or frustration. Robert Burton, in his "Anatomy of Melancholy" almost 400 years ago observed that humour purges the blood, making the body young, lively and fit for any manner of employment. Mirth is the principal engine for battering the walls of melancholy, and a sufficient cure in itself.

Sigmund Freud believed that mirth was a highly useful way of counteracting nervous tension, and that humour could be used as effective therapy.

Sir William Osler regarded laughter as the "music of life" and that people could keep themselves young with laughter.

Dr. Norman Cousins, a medical doctor himself, has written in an article in 1976 in the 'New England Journal of Medicine', how he cured himself of ankylosing spondylitis with a combination of laughter, vitamin C and an understanding physician. He has stressed the importance of people mobilizing their innate self-healing powers. Patient has the responsibility and power to become and remain well, and the healer acts only as a teacher and facilitator.

An interesting study was reported in *Science* (USA) in 1984 on patients who underwent gall bladder surgery in a hospital. 23 patients assigned to rooms with windows looking out on natural scenery had

shorter post-operative hospital stays, needed fewer potent analgesics and received fewer negative evaluation comments in nurses' reports than 23 matched patients in similar rooms with windows facing a brick building wall. Apparently, natural scenery elicits positive feelings, holds interest, reduces fear in stressed subjects and may block or reduce stress and anxiety.

Just as the negative emotions of fear, hate, anger, jealousy, greed, frustration are life-destroying, the positive emotions of love, hope, confidence, faith, creativity and the will to live and help others to live, would contribute to health and well-being.

An important message of Ayurveda is that health, instead of being "provided" or "delivered", has to be *practised* by *"Swastha Vrutta"* and *"Sad Vrutta"*. As individuals, we have the power and responsibility to keep our body and mind healthy by observing a number of simple rules of conduct and behaviour in relation to food, exercise, sleep, personal cleanliness, and by rules of ethical and moral conduct.

Many health problems arise from socio-economic and political factors that can be modified only by collective action. Individual responsibility has to be accompanied by social responsibility. The aim of health education is to make people understand how their behaviour and their environment affect their health, to promote "wellness" and to prevent disease through proper nutrition, exercise and healthful lifestyle, and to teach how to cope up with stress in their daily lives. An integral part of the doctor-patient relationship is to educate the patient about the nature and meaning of the illness, and about the possibilities of changing the patterns in the patient's life that have led to it. This in fact, is the meaning of the word *doctor,* which comes from Latin *docere* (to teach). The essence of good medical practice is the health education for promotion of positive health and prevention of disease, as well as care of the ill. It must be admitted that most of us have neglected this aspect of "doctoring".

Chapter 13

UNDERSTANDING MENTAL ILLNESS

Introduction

Understanding of the mind is the central problem for man. Religious and political beliefs, scientific and cultural advances, the evaluation of life and man's part in life all depend upon concepts, products of the mind. Ancient Indian thinkers and Philosophers have laid great stress on *'Atmanam Viddhi'* or *'Know thyself'*.

One's own mind is subjective experience, a personal world which can be explored only by *introspection*. The minds of other persons can be *inferred* from their behaviour, their speech, writing and actions. The minds of animals can be inferred from their actions alone.

We can only talk about the attributes of the mind. A pre-requisite for the phenomenon of mind is consciousness which may be described as a state in which there is ability to be aware of sensation — that is, a state in which perception may take place. Components of the mind (or mental process) can be considered as perception, memory, emotion, propositional thought and response. Since the end-products of the mind are apparent only in so far as they can be expressed in speech, writing or other action which together constitute *"behaviour"* in a broad sense, modern scientific study of the mind has mainly concentrated on the study of behaviour. Past and present patterns of behaviour create an image of the subject as *"personality"*.

The brain is the organ of the mind and till recently psychology attempted to treat the brain as a black box. Indeed, much of biology was learnt by the black box method. The difficulty with the black box approach is that unless the box is inherently very simple, a stage is soon reached where several rival theories all explain the observed results equally well. Attempts to decide among them often prove unsuccessful. In the last three decades, scientists have been able to poke inside the black box and gain valuable insights.

The complexity of the brain is yielding to scientific analysis and new pathways are being opened to the study of behaviour. The recent discovery of several neuropeptides and study of their possible functional roles is one of the most active areas of scientific research and is at the frontier of work in neurobiology.

The recent development of PET (Positron emission tomography) and appropriate radioactive tracers labelled with positron-emitting radionuclides has now made it possible to relate regional biochemistry within the human brain to measurements of behaviour in normal subjects and to elucidate abnormalities in patients with Alzheimer's disease, Huntington's disease, depression and multiple-infarct dementia (see also: Chemistry of behaviour, in chapter 7 — Chemistry of Life.)

There is a growing realisation that much of the world's burden of illness is *behaviour-related.* Major institutions concerned with the science base for health have increasingly addressed the relation of behaviour to health. The World Health Organization is actively planning a new programme of research on health and behaviour in developing countries. This chapter therefore, attemps to review our current understanding of human behaviour in health and illness.

Understanding Human Behaviour

What a piece of work is man! How noble in reason! How infinite in faculty! In form, in moving, how express and admirable! In action how like an angel! In apprehension how like a God! The beauty of the world! the paragon of animals!

Shakespeare, *Hamlet* — Act II Scene II.

Man, "the paragon of animals", scales the heights and plumbs the depths in his behaviour. The study of human behaviour has always interested scientists from the time of Charaka and Sushruta. The science of psychology tries to understand human behaviour in all its forms. How are we to understand what other people do, think and feel? How are we to understand ourselves? There are no easy answers to these questions. The promise of psychology is that rational means will give us a sure guide to understanding human behaviour.

In *Charaka Samhita* we find the earliest attempts to classify human behaviour.

Behavioral Types in 'Charaka Samhita'

In *Charaka Samhita,* Sharira Sthana, chapter IV, there is a detailed account of the varieties of human mind: "the minds of three kinds — *Sattvic* (pure), *Rajasik* (passionate) and *tamasik* (ignorant)": the pure mind is considered to be without any taint as it represents the beneficial aspects of the intelligence. The passionate mind is tainted as it represents the violent aspect. The ignorant mind is also tainted on account of its representing the deluded aspect.

Each of these three types of mind reveals an infinite number of variations on account of the differentiating factors of degree, origin and body, and the mutual concomitance of body and mind; thus a particular type of body goes with a particular type of mind; and conversely a particular type of mind with a particular type of body. Some samples are given below:

"One who is pure, devoted to truth, self-controlled, of right discrimination, endowed with knowledge, understanding and power of exposition and reply, possessed of memory, free from desire, anger, greed, conceit, infatuation, envy, dejection and intolerance, and equally well disposed to all creatures is the *'Brahma'* type".

"One who commands status, honour, luxuries and attendants, who is devoted to the constant pursuit of virtue, wealth and pleasure, who is clean and given to pleasures of recreation and whose modes of anger and favour are patent is the *'Kubera'* type.

"One who is fond of dance, song, music and praise, and is well versed in poetry, literature, history and legend, who is constantly addicted to the pleasures of fragrant flowers, women and recreation and is free from envy is the *'Gandharva'* type"."Thus the *sattvic* type is of seven varieties *(Brahma, Rushi, Indra, Yama, Varuna, Kubera and Gandharva)* all of these are the beneficent types, of which the most perfect mind is *Brahma."*

"One who is valiant, despotic, of an envious disposition, possessed of authority, given to poses, terrifying, pitiless and fond of self-adulation is the *'Asura'* type.

"One who is intolerant, of implacable hate, bides his time and then strikes, is cruel, gluttonous, inordinately fond of fleshy foods, of an excessively somnolent and indolent disposition and envious, is the *'Rakshasa'* type.

"One who is a great eater, luxurious, fond of keeping company of women in secret, unclean, a hater of cleanliness, a coward, a bully, given to abnormal recreations and foods is a *'Pishachya'".*

"One who is fond of food, whose character, conduct and pastimes are of a very painful description, who is very covetous, envious and without discrimination and who is disinclined to work is the *Preta* type." Thus the *Rajasa* type comprises of six varieties: *Asura, Rakshasà, Pishachya, Sarpa, Preta, Sakuna;* they are all tinged with passion.

"One who is of a forbidding disposition, unintellectual, disgusting in his behaviour and food habits, abandoned to sex pleasures, and given to somnolent habits is the *Animal* type."

"One who is pusillanimous, unintelligent, greedy for food, unstable, of persistent likes and dislikes, of itinerant habits and fond of water belongs to the *Fish* type."

"One who is lazy, exclusively devoted to the business of eating and devoid of mental faculties belongs to the *Vegetable* type."

"Thus the *tamasa* type comprises of three varieties—Animal, Fish and Vegetable. They represent the inert aspect of mind".

"Similar to the office of God in the world is the might of the individual soul in man. God's greatness in the universe is seen as creator; in the human body the soul's greatness is seen as the mind".

Evolution of Modern Psychology

In the late 1800's and early 1900's as psychology evolved from philosophy, Schools and "isms" of psychology grew up to provide their own answers to the question, how should we study human behaviour? One school, *Structuralism,* perhaps influenced by the chemistry of its day, started a search for the elements into which mind could be analysed. For example, a subject was trained to "introspect" what he experienced when exposed to a certain stimulus such as a coloured light, a tone, an odour, and describe it as minutely as possible. The structuralists hoped that in this way the elements of experience would be discovered. Although the "elements" approach of structuralism has disappeared, the interest in mind has persisted in psychology.

Another school, *functionalism* tried to study the adaptive functions of behaviour and mental life, not merely the structure of the mind. *Behaviorism* as it was originally developed in the tens and twenties of this century by John B. Watson (1878 – 1958) rejected the introspective method completely and insisted that psychology be restricted to the study of behaviour, the things people and animals do. The study of behaviour has remained a dominant theme in psychology.

Another school, *Gestalt psychology* was developed in Germany in the early 1900's. According to this school our experiences and behaviour are patterns or organizations analogous to a magnetic field, in which events in one part of the field are influenced by events in another part. For example a grey piece of paper is grey only *in relation* to its background or to something with which it is compared. On a black background it appears light; against a white background it appears dark. It is this stress on the relationships between elements that characterized Gestalt psychology. According to it, "the whole (experience) is more than the sum of its parts (elements)".

While these schools were developing within psychology itself, *psychoanalysis* originated within psychiatric practice. Sigmund Freud (1865-1939) developed a method of treatment and a theory of personality, based on his experience with neurotic patients. The emphasis of this treatment is on free association—the patient freely associates, or thinks and says whatever comes to mind. The psychoanalyst uses these free associations to analyse and understand the sources of the patients' problems. The theory of personality elaborated by Freud is quite elaborate, stressing the role of motives that are often repressed (not recognized by the individual and other people).

Modern behaviorists like B. F. Skinner stress that it is the *observable behaviour* that counts. Information about human and animal behaviour is gained by controlled experiments and observations rather than by more subjective or intuitive methods, which may only lead to fictional explanations of behaviour. Behaviorism attempts to demonstrate that human and animal behaviour can be predicted, controlled, and understood without recourse to explanations involving the "mind".

In recent years some psychologists have argued that the reductionist approach (breaking down of the whole into its component parts for the purpose of analysis) cannot give us an understanding of the individual as a whole. This viewpoint, *humanistic psychology* developed in the early 1960's as a reaction against the totally reductionist, observation-based analysis of human behaviour. Charlotte Bühler points out that "existential" considerations form the underlying philosophical basis of humanistic psychology. She believes that a totally objective approach to studying human behaviour overlooks the internal, integrative constituents of a person's total self—motives, wishes, internal conflicts, feelings, realizations and so on. Humanistic psychology tries to plumb a person's total self by conceptualising processes within the individual. Needless to say, the merits of this

approach as an alternative to empirical reductionist approaches is questioned by the behaviorists.

Species-specific Behaviour Patterns

The impact of the Darwinian theory of evolution on psychologists' thinking has been that *behaviour, as well as structure, evolves.* Many adaptive changes help the individual and the species fit better into some niche, or special habitat, within an environment. A small change in behaviour, like a small change in structure, may make an animal species more suited for life in some niche. The adaptive changes in behaviour will be selected so that they become part of the species' heritage in the same way that certain adaptive structures do. The important point to be appreciated is that species-specific behaviours *evolve* just as do structures. In the last 40 years the study of animal behaviour has been spurred on by the development of *ethology,* a subfield of zoology that studies animal behaviour from a biological point of view. The pioneer ethologists Konrad Lorenz, Niko Tinbergen and K. Von Frisch (who jointly won a Nobel Prize in 1973) have brought to us an appreciation on the great importance of species-specific behaviour in the adaptation of animals to their environment.

Although species-specific behaviour is genetically based, environmental factors play a role in its expression. Responses controlled entirely by genetic factors might be called instinctive, but since environmental influences continually modify the expression of genetically-based responses it is difficult to find true instincts, hence behaviorists prefer the term "species-specific" to "instinct". As evolution has proceeded, the nervous systems of animals have become more and more complex. The behaviour of higher animals has come to be controlled more and more by the unique experiences and environments they encounter. *Learning* and *reasoning* have become more and more important especially for human species. However, recent books by Konrad Lorenz, Desmond Morris and Robert Ardrey have made us wonder again about our animal nature. There is some biological basis for aggressive behaviour but this biological potentiality does not inevitably direct man to kill or destroy. The important question is, to what extent can educational measures direct man's behaviour into productive rather than destructive endeavours.

Emotional expression as a form of species-specific behaviour has been much studied since the time of Darwin. Expressions tell other members of the species about an individual's emotional state, and they

are sometimes considered to be incipient movements of attack or flight—the so-called intention movements.

Man's evolutionary heritage expresses itself behaviorally in a more general way. This heritage has resulted in the development of a nervous system that sets limits on, and provides potentialities for, our behaviour. Because of elaborate development of certain parts of the cerebral cortex, we are the species of animal best able to represent the world in symbols. We do this in speech and in visual imagery for the most part. Related to our ability to symbolize events is the ability to think about our world and ourselves in it. Each of us is aware that he is different from other people, and all of us try to fit our experience into some meaningful framework. We construct philosophies in our effort to explain ourselves and our place in the world.

Many other potentialities for behaviour are made possible by functional capacities built into the human brain through evolution. It has been shown experimentally that electrical stimulation of the limbic system leads to aggressive outbursts. Tumours in this region can also lead to aggressive behaviour. On the other hand aggressive behaviour is inhibited by electrical stimulation of other portions of the limbic system. Hunger, thirst, sexual behaviour also have specific controlling centres in the brain.

Chromosomes and Behaviour

Most of the behavioral traits that interest psychologists are determined by many genes, and it is not possible to pinpoint the particular gene responsible. But it is possible to show that certain chromosomes are necessary for the development of complex behaviours in both animals and humans. For instance, Down's syndrome (Trisomy of No. 21 Chromosome) is associated with severe mental retardation. Antisocial behaviour related to 47 XYY chromosomal pattern has attracted great interest. There seems to be a greater proportion of 47 XYY men in institutions for the criminally insane, than in normal population and in ordinary prison population.

Human intelligence is determined by multiple genes. The strongest evidence for a genetic basis of human intelligence comes from two types of study: (1) comparison of monozygotic or identical twins reared together or apart, and (2) correlation between foster-parents and their foster-children. The average correlation between pairs of identical twins reared apart is quite high, although it is lower than for

identical twins reared together. The influence of environment is brought out in the second type of study.

If we have so much trouble assessing the role of genetics and environment in twin studies, it is small wonder that we have far greater difficulty with racial studies. In a controversial article published in the *Harvard Education Review* in 1969, Arthur R. Jensen a professor of educational psychology at Berkeley U.S.A. reported that blacks as a group score significantly lower (about 15 points) on IQ tests than whites. Jensen attributed 80 per cent of an Individual's intellectual potential to genetic inheritance and only 20 per cent to environmental factors. These conclusions have been hotly disputed by others. Most of Jensen's critics, including the geneticist Joshua Lederberg, Nobel Prize winner, hold that culture, not race determines a man's intellectual potential.

The Genetics of Personality & Temperament

Personality is a difficult concept to define but it is made up of various distinctive and enduring traits that are characteristic of a particular person. We differ from each other behaviourally in many ways: in the expression of emotions, in motivations, interests, attitudes; in tendencies towards behaviour disorders; in the ways we protect ourselves against stress, guilt, fear and anxiety. Temperament is that aspect of personality which has to do with emotionality—a person's ease of emotional arousal, his characteristic forms of emotional expressions and his typical mood states.

Environmental factors, especially the learning experiences of people, play a very large role in shaping personality. Evidence for the inheritance of human personality traits is rather weak. There is much stronger evidence for the inheritance of certain abnormal personality traits. Heredity undoubtedly plays a role in chronic alcoholism, manic-depressive psychosis, schizophrenia. This evidence comes from the analysis of concordance rates for monozygotic and dizygotic twins. If schizoid behaviour disorders are considered along with schizophrenic disorders, the case for a genetic basis of this type of behaviour disorder becomes even more convincing.

Studies which change the environment, or nurture, by impoverishing or enriching it, attempt to unravel the intertwined factors of nature and nurture. The impoverishment studies have shown that for some behaviours there is a *critical period* during which certain environmental features must be present if the behaviour is to develop.

Social Development

Getting along with others is one of the most important things people do in our complex social world. The origins of each person's social behaviour go back to the earliest days of infancy. The first social responses are to be found in the attachment of babies to their mothers in the first few days and weeks of life. Attachment has great adaptive value because it keeps the infant close to the mother, where he or she can be fed and sheltered from harm. But as babies grow, they cannot remain tied to mother; they detach themselves to explore the environment. So the first theme in the development of human social behaviour is the attachment—detachment story.

As children grow older they meet many other people and getting along with others becomes the compelling, and continuing, theme of social development. Development of both positive and negative aspects of getting along with others – altruism and aggression – are of great importance. Another crucial aspect of social growth is moral development – ideas of what is right and wrong. As moral ideas develop, they come to be important in determining our responses to others.

Harriet L. Rheingold, a developmental psychologist has shown that sharing behaviour is observed in 18-month old children and perhaps even younger children. She speculates that this sharing behaviour may originate as a result of the many things that are shared with the infant during its early dependency on others. In addition, sharing behaviour probably develops as a result of both subtle and not-so-subtle rewards received for it. Unfortunately many of life's experiences work to thwart this development. Rheingold believes that society's task is to learn "how to build upon that generous nature" which infants develop b... which can be lost.

As children grow older, parents and other children come to shape their behaviour more and more. Social behaviour is very much determined by particular experiences that children have. Parents who provide models of pro-social behaviour (helpfulness, co-operation and altruistic behaviour), who reward pro-social behaviour, and who give their children practice in it can expect to have helpful, co-operative and altruistic children. Unfortunately, the reverse of this statement is also true.

In getting along with others, children must learn to curb their aggressive tendencies and to express them at appropriate times in socially approved ways. Things that parents do will either increase or decrease

aggressive behaviour in their children. Aggression is often, though not always, caused by frustration. As with pro-social behaviour, learning and modelling have a great influence on aggressive behaviour. Experiments have shown that if aggressive behaviour is rewarded, it will occur frequently. Furthermore, aggressive behaviour learned in one situation will generalise or spread to other situations.

Ultimately, much of a child's social behaviour as also that of the adult, is determined by ethical and moral ideas about what is right and what is wrong. Moral development, like cognitive development, seems to move through levels and stages. At the first level the child has little true moral feeling, and behaviour is dominated by selfishness and deference to superior authority. At the second level ethical ideas are dominated by conventions and a law-and-order orientation. At the third, abstract principles of law or human dignity govern ethical decisions. If the future lies with the world's children, the world's urgent problem is how to provide environments that do not limit children's moral development.

Principles of Learning

Learning is the key process in human behaviour. Learning can be defined as any relatively permanent change in behaviour which occurs as a result of practice or experience. It pervades everything we do and think. *Socialization* is the name given to the learning processes through which the infant is trained in the attitudes, beliefs and behaviours appropriate to his culture. Training reinforces the behaviours desired, and extinguishes the others. Learning takes place in many different kinds of situations. We will discuss four learning situations: (1) classical conditioning (2) operant conditioning (3) cognitive learning (4) punishment and negative reinforcement. In the first two, positive reinforcement (reward) is typically used to promote learning. In the third, learning takes place without reinforcement. The fourth is somewhat like the first two except that negative reinforcement (unpleasant stimulation) is used to promote learning.

Ivan Pavlov (1849 – 1936), the famous Russian physiologist introduced the concept of conditioning and established many of its basic principles. Pavlov discovered very early that if he conditioned an animal to salivate at the sound of a bell, it would also salivate, though not quite so much, at the sound of a buzzer or the beat of a metronome. The animal tended to *generalize* the conditioned response

to stimuli that were different from, but somewhat similar to, the one to which it was specifically conditioned.

Many human responses and characteristics seem to be acquired through the process of *conditioning and generalization.* The greater the similarity between stimuli the greater the generalization between them. People develop fears and phobias by acquiring them through accidental conditioning to some stimulus and then generalize them to situations that otherwise would not be frightening. It is the emotional responses which become conditioned to certain stimuli that are important in human life.

Reinforcement is the key term to understand operant conditioning. "Well done!" from the boss, is an example of reinforcement. The word 'operant' signifies that when a response operates on the environment in the appropriate fashion, a reinforcer or strengthener of the tendency to make that response is forthcoming. Many attitudes and beliefs, customs, learned goals and certain aspects of the use of language can result from shaping behaviour by means of reinforcement, through the mechanisms of operant conditioning. B. F. Skinner in a book entitled "Science and Human Behaviour" has pointed out the importance of operant conditioning in the socialization process.

Besides being ever-present in human situations, operant conditioning is sometimes deliberately used to shape desired behaviours. Programmed learning and certain types of therapy for behaviour disorders are examples. Behaviour therapy is an attempt to treat behaviour disorders by reinforcing socially adaptive behaviour and extinguishing maladaptive behaviour.

There is some evidence that visceral responses such as heart rate, intestinal contractions and blood vessel dilatation can be operantly conditioned. This has promising implications in the treatment of many problems like high blood pressure.

Social Motives

The social motives are the complex motive states or needs, that are the well-springs of most human actions. Three of the most studied social motives are the *need for achievement, need for affiliation* and *need for power and status.* Motives are inferred from behaviour. Measurement of social motives can be done by various techniques such as projective techniques, questionnaires or inventories, observations of actual behaviours in certain types of situations designed to bring out the expression of

social motives, and analysis of the literary and artistic output of an entire society in order to get an idea of the main social motives of its people at a particular time in history.

The best known projective tests are the Rorschach Inkblot Test and the Thematic Appreciation Test (TAT) which consists of pictures of scenes and people.

Knowledge of the social motives dominant in a society may help us understand its history and predict its future. This application of psychology to history and contemporary political trends is relatively new but it may turn out to be a major contribution.

The course of motivations does not always run smoothly. Things happen to prevent us from reaching the goals towards which we are driven. This leads to frustration, depression, anxiety, guilt or anger. Generally speaking, the causes of frustration are to be found in environmental forces that block motive fulfilment, personal inadequacies that make it impossible to reach goals, and conflict between motives.

Frustrations

Of the three general sources of frustrations described above, motive conflict is the most important in determining a person's anxieties, or "hang-ups". Three major kinds of conflict have been identified, called approach—approach, avoidance—avoidance, and approach—avoidance.

Approach—approach conflict occurs between two positive goals that are equally attractive at the same time. The proverbial donkey starved to death because it stood halfway between two piles of hay and could not decide which to choose. Such a conflict is usually resolved by satisfying one goal first, then the other, for instance, eating and then going to bed if a person is both hungry and sleepy—or by choosing one goal and giving up the other. Compared to other conflict situations, approach—approach conflicts are easy to resolve and generate little emotional behaviour.

Avoidance—avoidance conflict is a fairly common experience, like being caught between the devil and the deep blue sea. We can all think of things we do not want to do but must do, or face even less desirable alternatives. Vacillation and attempt to leave the conflict situation are two kinds of behaviours emerging in such a situation. People in avoidance—avoidance conflicts may try a different means of running away. They often rely on imagination to free them from the fear and anxiety generated by the conflict. They may spend much of their time

in day-dreaming—conjuring up an imaginary world or regressing into a childhood fantasy. Many intense emotions are generated in avoidance—avoidance conflicts—fear, resentment, anger at being trapped in a situation where the goals are negative.

Approach—avoidance conflict is often the most difficult to resolve. In this kind of conflict a person is repelled and attracted by the same goal object. A young bride for instance, may have been brought up in an atmosphere where sex was treated as ugly and sinful. At the same time, her normal sex drive as well as other social values involved in marriage, give the marital situation a positive valence. Caught between conflicting sexual motives, social motives and attitudes learned in childhood, she experiences anxiety. The obstacles to the satisfaction of motives may be *internal* (like values acquired in childhood), hence much more difficult to handle than external obstacles. Coping with the emotional reactions caused by such an internal conflict can create major problems of adjustment. In the human motives there is a constant struggle between *"Shreyas"* (what is the right thing to do) and *"Preyas"* (what one would love to do).

Common Conflicts

Owing to the number of needs that people have and the many ways of satisfying them, all sorts of frustrations and conflicts are possible. Conflict is likely to occur whenever pleasure and pain, or reward and punishment, are associated with the same thing. In different cultures and at different times completely different patterns of conflict may be seen.

Achievement need versus fear of failure, independence versus affiliation needs, sexual desire versus fear of sex, hostility versus need for social approval are common conflicts in many cultures. There are almost as many sources of conflict as there are motives, situations and people.

Development of Attitudes

From birth to puberty a child's attitudes are shaped primarily by his or her parents. Parental influences wane as children grow older, and other social influences become increasingly important with the beginning of adolescence. During the period from 12 to 30, most of a person's attitudes take final form and thereafter change little. During the critical period three main factors are at work: peer influences, information from news media, and other sources, and education. Of all the three

factors, education stands out consistently. The more educated people are, the more liberal their attitude.

Is there indeed a generation gap? Many studies show that there are indeed differences in attitudes between two generations. Social scientists think that differences of opinion between today's youth and their parents are ideological rather than generational.

Although their general attitudes may be well formed, adults are continually acquiring new attitudes, or changing their attitudes towards specific people and objects. Through advertising, political campaigns and many other means, a great barrage of attitude-shaping messages is directed at us day in and day out. There are three principal aspects of any situation in which attitude change is attempted, the source of the message, the message itself and the characteristics of the recipient.

Three characteristics of the source of message strongly affect our response—credibility, attractiveness and power.

As regards the message, advertisers and propagandists often rely on *suggestion* or the uncritical acceptance of a statement, without requiring facts. The most common form of suggestion is prestige suggestion, in which the message appeals to people's regard for authority or prestige. *Appeal to fear* is another method to persuade people. The use of *loaded words* is another technique.

Certain characteristics of the person receiving a message influence its effectiveness: his influenceability, his needs and goals, selective interpretation, avoidance of threatening information, and prior "immunization" by mild arguments.

Prejudice refers to an unjustified attitude, usually unfavourable. Discrimination often results from prejudice. It is the behaviour of treating a person or a group in an unfavourable way. The factors that help to minimise prejudice are acquaintance potential, equal status, friendly association, co-operative rewards, and similar personality characteristics.

Defense mechanisms and Coping behaviour

Freud described a number of ways in which people typically behave to avoid or lessen anxiety. These he called *defense mechanisms.* Many psychologists now do not accept Freud's theories, but they do accept these mechanisms as descriptions of the way people behave in coping with their problems.

Forgetting *(repression)* is a refusal to think about something because we find the thought unpleasant. If we don't think about it, we don't rehearse it—which is what we need to do to preserve something in long-term memory—and so we forget it.

Reversing motives *(reaction formation)* like being too modest, too solicitous, or too affectionate to disguise the opposite feeling. A quotation from Shakespeare captures the idea of reaction formation: "The lady doth protest too much, methinks".

Blaming others *(projection)* is a common coping mechanism. Carried to the extreme, projection is the mark of the behaviour disorder paranoia. The paranoid has projected his own hostile feeling about others into a whole system of thinking in which he feels that others are out to get him.

Making excuses *(rationalization)* is another kind of coping behaviour in which an acceptable motive is substituted for an unacceptable one. We give a different reason from the real one for what we are doing. 'Sour grapes' is another version of rationalism—something which we cannot get becomes something we did not want anyway.

Kicking the dog *(displacement)*—in this coping behaviour, the motive remains unaltered but the person distorts the goal of the motive by substituting a different goal object for the correct one. Most often the motive of displacement is aggression, which for some reason the person cannot vent on the "true" object.

Fantasy or day-dreaming is a coping pattern in which a person resolves conflicts by simply fleeing them — or trying to. Fantasy is very common, especially among adolescents. Upto a point it is a harmless way of getting some satisfaction by temporarily escaping from reality (like a boy who is not popular with girls but wants to be, conjures up a fantasy in which he is a Don Juan). But it rarely leads to constructive action.

Identification with some one else is another way of coping with frustration. Becoming friends with an important person, for example, can make us feel important. Youths often identify with popular film stars, wearing the same kinds of clothes, trying to talk in the same manner and so on. In this way, they secure some of the satisfaction their model enjoys which they themselves would not have.

Acting childish *(regression)* is often seen in children 4 or 5 years old because at this age they begin to face an increasingly complex set of frustrations. In regression the child frequently reverts to baby talk and

to all sorts of 2-year-old behaviour. Adults too sometimes revert to childish behaviour when they are unable to find an "adult" way of approaching a problem.

Compensation: here a person finds a substitute activity to satisfy a social motive. Failure or loss of self-esteem in one activity is made up by efforts in other areas. The unattractive girl may become a book worm and eventually a distinguished scholar thereby commanding the respect and prestige that she was unable to win with good looks. Life is full of compensations through which people achieve satisfactions that they might not obtain otherwise.

Almost everyone resorts to defense mechanism at one time or another, and when they are used sparingly for minor conflicts, they are nothing to worry about if they do not damage other people. If they allow us to feel more comfortable at times, as they often do, then they have served a useful purpose in restoring our mental equilibrium. But if a person comes to depend on them, these defensive attempts to cope with problems are harmful. They never solve real problems; they only allay anxiety about them. Even more seriously, defensive behaviour often does not dispel anxiety. If certain situations make us anxious, we will meet them time and again and sooner or later come up against one for which we have no defense.

Behaviour Disorders

A behaviour disorder is some pattern of abnormal behaviour. "Abnormal" however is difficult to define. The fact is that there is no behaviour which is abnormal in itself. Behaviour exists on a continuum. When a person shows complete lack of behaviour that is seen in most people, it is abnormal.

Ten years back, D. L. Rosenhan, a professor of psychology and law at Stanford University thought that diagnoses of behavioral abnormality are based on less substantial grounds than most people realize. He therefore conducted an experiment in which eight *sane* people (3 female and 5 male pseudo-patients) gained admission to a variety of hospitals. Beyond giving phony symptoms like "hearing voices", that said "empty, hollow and thud", and concealing the fact that they were psychological researchers, the pseudo-patients told the truth and acted normally. They answered all the questions about their past experiences honestly. And though their symptoms were preposterous, they were admitted to the psychiatric wards of every hospital they went to. Once in the hospital, each pseudo-patient stopped pretending

to have any abnormal symptoms. Their task now was to get out of the hospital by convincing the staff that he or she was sane. On the average it took pseudo-patients *19 days* to be discharged from a hospital. Each however, was discharged with a diagnosis of "Schizophrenia in remission". This means that in the hospital's view the patient was not normal, and had not been, upon admission. Such a diagnosis carries personal, legal and social stigmas, yet there was a uniform failure by institutional personnel to question their conclusions, much less to recognize that the pseudo-patients were normal and sane.

Oddly, other patients in the wards often did suspect that the pseudo-patients were sane. One reason why the hospital personnel did not, is that patients are not carefully observed by the staff in psychiatric hospitals. In fact, psychiatrists were rarely seen in the wards. Failure to detect sanity may also be due to the fact that *physicians operate with a strong bias towards calling a healthy person sick,* rather than vice versa. Rosenhan concluded that any diagnostic process which lends itself to such errors needs review.

Psychoneurotic Disorders

People suffering from "neuroses" or "psychoneuroses" are anxious people. Often their anxiety is obvious. They may be constantly apprehensive and worried, or full of complaints about themselves or about the world. But sometimes the anxiety is not so obvious; the person may appear relatively free of it, yet show reactions that can be traced to anxiety and the learned avoidance of it. Indeed the principles of learning, discussed earlier, are important in understanding psychoneurotic disorders.

Conversion reactions are a learned behaviour which enables the patient to avoid or escape from the intolerable and insoluble anxiety-producing situations. The soldier with "combat fatigue" is an example. Some soldiers in an avoidance—avoidance conflict situation, where they risk death if they obey commands, and incur disgrace or imprisonment if they do not, develop symptoms that resolve the conflict by removing them from the whole situation. For instance the soldier might become paralysed so that he is no longer fit for combat. But he is not consciously malingering—he really cannot move although nothing is wrong with the muscles and nerves.

The symptoms of conversion reactions do not have a biological cause; they are not caused by a lesion, a germ or other detectable

physical agency. The ailment which is real enough, however, is a device for coping with conflict and anxiety. Similarly, when a patient improves markedly on a placebo, we do not accuse him of faking. He has experienced real physical discomfort and his expectations of the power of the drug have led to real improvement.

Dissociative reactions are in a mild form, a normal pattern of behaviour shown by many people. The college student who cusses and jokes in the common room, but becomes serious when talking to her lover's parents, seems to display two different personalities. In a relatively harmless form, dissociative reactions may involve no more than a compartmentalization of a person's thinking and way of living. In the more extreme forms, dissociation reactions are incapacitating.

Amnesia is one well-publicized type of extreme dissociative reaction. In Amnesia as a neurotic disorder the person may forget his own name, where he has come from, who his relatives are, and what he has been doing for weeks, months or years.

Multiple personality is another dramatic form of dissociative response, in which a person's system of memories and traits seems to dissociate into two or more complete personalities. Typical example is the fictional case of Dr. Jekyll and Mr. Hyde. The change is triggered by stress or emotional trauma and it stems from a deep-seated conflict of motives.

Phobic Reactions

Some people who are otherwise normal and healthy have phobias or fear of small places, high places, the dark, animals and so on. The phobia may be so powerful and irrational that it alters the whole course of the person's life. Phobias may have their origins in fears learned by association of painful or unpleasant events with particular situations. Although the fear is rational when initially learnt, it subsequently diffuses. This is an example of stimulus generalization. There is no qualitative difference between a rational and irrational fear; the distinction is based on how society perceives the fear.

Obsessive Compulsive Reactions

An *obsession* is defined as un unwanted idea that constantly intrudes into a person's thoughts, while a *compulsion* is an act that constantly intrudes into a person's behaviour. Both may be regarded as operant behaviours. One compulsive person must wash his hands every few

minutes; another must count all the steps she climbs. Some people are compulsive in a more general way; they find ambiguity and uncertainty extremely uncomfortable, and they strive for orderliness in thought, dress and in work. Indeed any unusual emphasis on "doing things the right way" may be regarded as compulsive.

Depressive Reactions

A certain amount of depressive behaviour is considered normal in our society. When a spouse dies, or when a loved relationship breaks up, the person is left without a source of reward (attention, affection, sex) for a great range of behaviours, the individual ceases to emit many of these behaviours because they no longer lead to reinforcement. Until the depressed patient learns new responses to replace the old, that is, new responses which bring reinforcement, his level of activity will be naturally low and his mood sad.

Ayurveda and Insanity

Charaka Samhita attributes insanity to vitiation of the humours. It is interesting that current research is focused on neurotransmitters like dopamine, noradrenaline and serotonin in relation to schizophrenia, depression and pre-senile dementia (Alzheimer's disease). Charaka described the symptomatology as under:

"Confusion of intellect, extreme fickleness of mind, agitation of the eyes, incoherence of speech, mental vacuity, unsteadiness, these are the general symptoms of insanity".

"Insanity which is characterized by such derangement of understanding, mind and memory, is of exogenous or endogenous origin".

"Possession by the Gods, sages, Gandharvas, Pisachas, Yakshas, Rakshasas and the manes, and the failure in the proper discharge of observances and vows in this life or the previous one—these are the causes of insanity of the exogenous type".

"Provoked Vata, Pitta and Kapha are the causes of insanity of the endogenous type".

Apart from various therapeutic measures for the treatment of insanity, Charaka states:

"If the patient continues to behave violently, then he should be made gentle by soft but strong bandages and put into a dark room free from metallic and wooden articles (lest he should harm himself with these).

"Flagellation and giving shock to the patient's mind, intellect and body are advised in difficult cases. Thus he may be terrorised by means of snakes whose fangs have been removed or by trained lions and elephants, or by men dressed as bandits or foemen with weapons in their hands or men impersonating the king's officers may, having dragged him out securely bonded, intimidate him with threats of immediate execution by the order of the king".

"It has been well said that the threat to life is more potent than fear of bodily injury; accordingly that measure may succeed in helping the disordered mind of the insane patient to regain its composure when all the other measures have failed".

"The man of strong mind, who abstains from flesh and alcohol, observes a wholesome diet and is always dutiful and pure, will never fall a victim to insanity, whether exogenous or endogenous".

Treatment of Behavioural Disorders

Hippocrates, the "Father of Medicine", around 300 BC, concluded that mental disorders arise from the same natural causes as physical ailments. According to Hippocrates, melancholia (depression) is caused by an imbalance of the body's four humours in which "black bile" ascends to the brain.

From time to time, religious notions have strongly influenced the treatment of the mentally ill. In the 10th and 11th century Europe, for instance, nearly all physicians were also clergymen, and the monastery served not only as a church but also as a university and mental hospital. Bizarre behaviours were sometimes viewed as signs of divine intervention, sometimes attributed to possession by demons. Exorcism was the logical treatment to rid the body of demons. Other remedies used included herbs, human and animal excrements, prayers and holy water, the breath and spits of priests, pilgrimages, relic handling, and lucky charms.

Later on, cruel treatments were devised for abnormal behaviour. The last part of the Middle Ages was marked by extremely violent treatment of behaviour disorders, including torture and burning at stakes. Belief in witchcraft, astrology and alchemy grew during the 13th and 14th centuries. As late as 1692 nineteen witches were executed in Salem, Massachusetts, USA.

By the end of the 19th century, religious interpretation of abnormal behaviour had gone out of favour. People returned to the earlier beliefs

that the behaviour disorders are like physical ailments, and that no one can be "blamed" for mental illness. Severely disturbed people were put into mental hospitals. But most patients received no treatment, and care and facilities in the hospitals were poor. Only in the early 20th century did conditions in mental hospitals begin to improve.

Psychotherapy was initiated by Freud who was himself a physician, and psychoanalysis through much of its history has been in the hands of physicians. Psychologists, in contrast to physicians, began to treat behavioral disorders only in the last three or four decades.

Over the years, a variety of medical therapies have been tried out with mental patients. Three principal methods in current use are ECT, psychosurgery and chemotherapy.

Electro-convulsive Therapy (ECT)

ECT was introduced in 1937 by Cerelleti and Bini. Since then it has been widely used in mental hospitals for the treatment of psychotic depressive states. In this procedure the patient lies on a table in a supine position and with the help of special electrodes, an alternate current of 110 volts is passed for less than a second between the temples, or, less frequently, between the vertex and the non-dominant hemisphere, till convulsions are produced. The patient awakens from the ECT with a headache and has no memory for the events that immediately preceded ECT. Generally 2-3 treatments are given in a week. A patient with depression requires on an average 4-8 treatments, while schizophronia needs about 10-20 treatments.

Antidepressant drugs have brought down the number of ECT procedures over the years. Antidepressant drugs are slow in action and take about 1-2 weeks for optimum response. The outstanding reason for ECT rather than drugs in severe depression is the lessened danger of suicide which rarely occurs after initiation of ECT. To prevent dislocations or fractures that may occasionally occur in ECT, use of muscle relaxants and anaesthetic agents is made, with endotracheal tube and oxygen always at hand. Modified current (200 milliamperes) for a brief duration seems to show better conservation of memory and better results on intelligence tests. Unilateral ECT over the non-dominant hemisphere shows similar results.

Psychosurgery

In 1933, Moniz, a Portuguese psychiatrist, originated the idea of performing brain surgery as a treatment for psychosis. He believed that

the fixed ideas and repetitive behaviour seen in some psychotic patients are accompanied by "abnormal stabilization of cellular connections", especially in the pre-frontal lobes of the brain. To "unstabilize" the connections he recommended severing or removing some of the brain tissue involved. The operation introduced by him, prefrontal lobotomy, severed the nerve pathways in the brain that connect the most forward parts of the frontal lobe with the underlying regions of the brain. Prefrontal lobotomy is rarely performed now since the advent of effective psycho-active drugs. Instead, psychosurgery on the centres for emotion has come into vogue.

On August 1,1966, a 25-year old man Charles Whitman climbed to the top of a town on the campus of the University of Texas at Austin and began firing at passers-by with a high-powered rifle, wounding 31 people and killing 13, before he was himself shot dead by the police. At autopsy on Whitman's body, a tumour in the temporal lobe was revealed. The temporal lobe is the area of the brain most often related to episodes of violent behaviour. Experimental stimulation of the particular part of the temporal lobe called medial amygdala causes loss of control and an outburst of rage. When another part of the amygdala is stimulated, a feeling of relaxation is produced. Based on these observations, Vernon Mark, a neurosurgeon and Frank Ervin, a psychiatrist introduced the idea of operatively destroying the medial amygdala. The operation reduces violent outbursts, but the patient may remain confused and delusional, and unable to work or care for himself. Evidently not enough is known about the ways in which the amygdala and other areas of the brain control aggressive behaviour. Many psychiatrists maintain that the value of psychosurgery has not been firmly established.

Chemotherapy

Different drugs affect different parts of the brain and thus affect the way the brain works. In recent years, 30 different small molecules functioning as Neurotransmitters have been identified and their distribution in different parts of the brain has also been studied. For instance the most widely used tranquillizers, the benzodiazepines (valium etc.) are shown to be active at the GABA (gamma aminobutyric acid) receptors which are mediators of the inhibitory neurons in the brain. Approximately 1/3 of neurons are inhibitory.

Phenothiazines act on the dopamine receptors. According to current hypothesis, an over-activity in the brain dopamine systems (particularly

in the limbic system, a region involved in emotional behaviour) may underlie the symptoms of schizophrenia. Amphetamine triggers the release of dopamine at nerve terminals and produces in high doses disruption of thought processes, hallucinations and delusions of persecution, symptoms very similar to those found in some forms of schizophrenia. Hallucinogenic drugs show a strong structural resemblance to the monoamine transmitters. Mescaline possesses the benzene ring structure of dopamine and noradrenaline; LSD incorporates the indole ring structure of serotonin.

The wide variety of anti-schizophrenic drugs that have been developed, such as chlorpromazine and haloperidol, share the property of binding tightly to dopamine receptors thereby preventing the natural transmitter from activating them. This discovery has proved to be one of the most promising leads in modern schizophrenia research. The latest evidence suggests that schizophrenia is associated with an over-production of dopamine or an over-responsiveness to the transmitter in certain regions of the brain.

Another important group of currently popular drugs are the *anti-depressants.* One category of drugs is represented by iproniazid and other drugs that inhibit the enzyme monoamine oxidase, which degrades noradrenaline, dopamine and serotonin. As a result of the blockage of this enzyme the arousing effects of those monoamines are enhanced, accounting for the anti-depressant actions of the drugs. A second category of anti-depressant drugs, the tricyclics, also amplify the effects of noradrenaline and serotonin in the brain. Those drugs, of which the best known are imipramine and amitriptyline, block the re-uptake of noradrenaline and serotonin from the synapse; the stimulant drug cocaine appears to work by the same mechanism. Such observations have suggested that depression may be associated with low levels of amine transmitters at brain synapses, whereas mania may be associated with excessively high levels of those transmitters.

The greatest benefit of these drugs is that they have largely eliminated the need for psychosurgery. They quieten down aggressive and over-reactive hospitalized patients without damaging the brain tissue irreversibly. Owing to the use of these drugs, many hospitals have now fewer restraints on mental patients (locked and barred rooms, straight jackets, isolation rooms). And hospital confinements are shorter because the patient's families are more willing to take them back home when they are calm and cooperative. The quiet and cooperative patient can be trained in the method of relaxing, of lowering

anxiety, and of mastering the conflicts of life. As people learn to modify their behaviour, their drug dosage can be gradually reduced and finally stopped.

Lithium and Mania

People suffering from mania or bipolar disorders (manic-depressive psychosis) often improve impressively when they are treated with salts of lithium.

Cade, a physician and psychiatrist in Australia in 1949, found in guineapig experiments that an injection of a solution of lithium carbonate made the animals extremely placid and lethargic and unresponsive. Cade speculated that the calming effect of lithium on guineapigs might be repeated in human beings. Oral administration of lithium salts to a 51-year old man who had been hospitalized with chronic mania for 5 years, showed such improvement that within two months he was able to leave the hospital and resume his job while remaining under lithium therapy.

Lithium is the third lightest element, following hydrogen and helium, in the periodic table of elements. It is fascinating that a simple salt, an ion, an extract of rock, is able to alter such an ephemeral and subtle property of mind as mood. People are more accustomed to the idea that states of feeling are affected by relatively complex organic substances such as opium, marijuana, cocaine and alcohol. The physico-chemical simplicity of lithium arouses the hope that it will shed light to clarify the neuronal basis of mood.

Psychotherapy

The term psychotherapy is conventionally limited to the form of treatment which depends upon direct and personal relationship between the patient and the physician. What the psychotherapist does, can be described by metaphor and analogy. He promotes the *ventilation* and *desensitization* of emotional disturbances; he *elucidates* latent or obvious muddles, *disentangles* conflicting tendencies, giving them new incentives and a different direction; and so guides the patient through the maze of his life's experience as recalled in memory, that he is better fitted for dealing with current experience, knows himself better, and has somewhat *"purged"* himself of past harms. All *"analytic"* methods review the patient's life as he recalls it under special conditions. e.g. of free association, hypnosis, biographical schemes etc.

Of late, much effort has been put into "group" psychotherapy rather than individual patients. The groups, usually of about 5 to 20 people, have a minimum of structure. In an atmosphere where facades are dropped and emotions are stressed, members work through their initial negative feelings, aggressive behaviour, and confrontations, and more positive feelings emerge; previously unloved, lonely people may begin to experience positive regard for others in the group.

The psychotherapies, as distinguished from behaviour modification, pay attention to the elements in the patient's problem: environmental barriers, personal frustrations, motivational conflicts, deeply rooted personality disorders, inadequate learning of necessary social skills or learning of inappropriate behaviours.

Psychoanalysis relies on the technique of free associations and dream analysis to help patients gain insight into their problems. Often a patient shows resistance in free association, then later develops transference to the analyst. The transference must be dissolved at the end of analysis.

The *existential therapist* tries to accept the patient as he is and to understand the ways the patient seeks for meaningfulness and value in life.

Client-centred therapy puts the patient in a permissive situation where he or she has freedom to explore and express attitudes, hopes and fears. The therapist does the minimum of interpretation.

Gestalt therapy attempts to get the patient to be more aware of his true self to allow his natural impulse to emerge.

Play therapy, used mainly for children, permits a child to release feelings without fear of reprisal.

Behaviour modification begins with a functional analysis of a person's behaviour, attempting to see what antecedents lead to the disordered behaviour and what consequences the behaviour produces. Then a particular form of therapy is chosen.

Various *operant conditioning techniques* may be used for behaviour modification. Among these are: the application of positive reinforcement for desired behaviour and the use of extinction or punishment for non-desired behaviour.

Token economics established in hospitals and outpatient clinics provide the patients with tokens as secondary reinforcements for doing desirable things. The tokens are later traded for something the patient wants.

The classical conditioning techniques of behaviour modification include *aversion therapy* to eliminate undesirable responses; *covert sensitization*, in which the patient imagines unpleasant things associated with his bad habits; and *systematic desensitization* in which the patient combats anxiety with deep muscular relaxation.

Modelling techniques of behaviour modification are based on observational learning. For example, a patient may lose a fear of snakes by watching someone else handling snakes.

Biofeedback techniques permit a patient to monitor his internal organs, such as heart or stomach and gain some control over their function.

Brain-washing

In the early 1950's a new word entered our vocabulary "brain-washing". As a result of the Korean War, American soldiers were exposed to "coercive persuasion" — an intensive indoctrination programme combined with sophisticated techniques for undermining the social structure of the captive group. Typically, the procedure consisted of first removing from the group anybody who showed signs of leadership. This robbed the "followers" of a source of emotional support they needed to maintain tolerance of stress. The remaining members were treated in different ways in order to foster guilt and suspicion among the captives and build mistrust among them. This procedure breaks down group cohesiveness and discourages personal interaction.

Under these conditions, as well as being underfed, physically tortured and isolated, some individuals were systematically brought to the point where they had to choose between maintaining their old attitudes and possibly not surviving internment. The prisoners became uncommunicative and non-committal about everything. Next, the indoctrinators began daily "instructions" in an attempt to induce co-operation from the men and try to change their attitudes about various things. Those who resisted were punished and those who behaved "correctly" were rewarded. The whole process was aimed at establishing a need for change and then providing a direction for the change.

Schein and his colleagues report that almost all the prisoners showed some compliance. Fewer than 5 per cent resisted the pressure with no discernible attitude change. For the most part, however, the prisoners' compliance consisted of *doing* what was expected of them. But later,

when the prisoners were released, only a very few appeared to have undergone any significant change in ideology. Thus coercion does not appear to be the best way to produce long-lasting changes in attitude; education is the best way, since, by definition, education is concerned with behaviour shaping and behaviour modification. Positive reinforcement is a more effective way than punishment or negative reinforcement, to elicit desirable behaviour.

Behaviour shaping

The social bonds established between the new-born and the mother within the first few hours or days of life are critical in shaping the primary adaptive social attitudes and social behaviour. The sense of security derived from the rhythm of the mother's heart-beat when she holds the baby in arms and the loving and affectionate care given in prompt, consistent, and confident manner, ensure normal emotional growth. Lack of care at this stage may result in life-long retreat, anxiety or hostility. The parent is the child's first and most important teacher or model, whom the child will imitate. The relationships established with parents in infancy are extended to other familial and extrafamilial contacts; love and affection, security, approval, encouragement, recognition and pride all facilitate normal emotional growth and development.

Maintenance of Mental Health

Mental health is a problem that concerns everyone. So many people suffer from behavioural disorders that we cannot escape some personal contact with them. Neurotic people undoubtedly make up the largest single group. Roughly five per cent of the adult population in our society consists of people who have been severely handicapped in social adjustments. Alcoholism and drug addiction, and anti-social behaviour, represent another kind of social maladjustment.

About half the hospital beds in the United States (as also United Kingdom) are occupied by mental patients, roughly constituting one million beds. As the number of old people in the population increases, the problem of senile psychosis is going to be aggravated. Senile psychotic behaviour is characterized by delusions, defects of memory and general dis-orientation. A person may imagine that he has been talking to someone who really was not there; he may forget what he has just said, at the same time insisting he remembers things which never happened. He may be disoriented in time and space. The brain

damage resulting in senile psychosis may be the result of cerebral atherosclerosis, hardening of the blood vessels that supply the brain, resulting in diminished blood circulation. Additionally, there is a loss of neurons due to ageing. The severity of the disability depends on the degree of brain damage as well as the person's skills and patterns of adapting to stress. For some people, mild brain damage is just another stress for which they may be able to compensate, depending upon previously learned adaptive skills.

Prescription for Mental Health

Charaka has emphasised good conduct as a means to maintaining mental health and happiness.

"Those who are desirous of their welfare both in this and the next world should suppress the rash and evil impulses of the mind, speech and body."

"The wise man should control the impulses of greed, grief, fear, anger, vanity, impudence, jealousy, excessive attachment and malice".

"One should control the impulse for speech that is harsh, extravagant, insinuating, untrue and untimely".

"One should control the impulses for all such activities of the body as are injurious to others, such as adultery, theft, inflicting pain etc.

Avoidable Men

"Those who are sinful of conduct, speech and disposition, back-biters, quarrelsome, sarcastic and niggardly; those who are envious of others' prosperity; those who are fickle minded, those who have a foot in the enemies' camp, those who are without compunction, all such, the scum of humanity, should be shunned".

Associable Men

"Those who are mature in understanding, learning, years, character, courage, memory and one-mindedness; those who frequent the company of such; those who are endowed with insight into the nature of things; those who are free of all ailments; those who are well-disposed towards all creatures; those who are tranquil of heart; those who are of commendable character; the teachers of the right path; and those who hear and see only that which is meritorious, are to be sought".

"The wise man who seeks happiness both here and hereafter, should exercise the highest care in selecting what is wholesome in the matter of food, conduct and behaviour".

Preservation of the Normalcy of the Mind

"The right, as well as excessive, deficient, and erroneous perceptions are the causes respectively of the order and disorder of the mind and understanding ".

"For preserving the normalcy of the mind and for protecting it from abnormality, efforts should be made by the following means: the wholesome contact of the sense organs and their objects, the proper performance of actions after intelligent and repeated scrutiny".

"Fellowship with all creatures, winning over the angry, consoling the frightened, befriending the destitute; bearing with harsh words from others, overcoming impatience, showing a tranquil disposition, and removing the causes of passion and aversion".

"Speak no untruth; take not away other's goods; covet not another's wife nor another's wealth; delight not in vengeance; sin not even against a sinner; expose not another's shortcomings; pry not into others' secrets; keep not the company of those who are irreligious, disloyal to the king, arrogant, deprived, mean and wicked. Do not speak ill of good people and your elders. Transgress not the majority decision; break not a rule; do not develop a taste for drinking, gambling and the company of prostitutes".

"Be neither timid nor overbold; be not ungenerous to your dependants; be not distrustful of your kinsmen; take not your pleasures alone; regard not the maintaining of character and social observances as a tax on you; do not trust everyone nor distrust everyone; be not always ruminative".

"Do not let slip the right moment for action; do not undertake anything without deliberation; do not be a slave to your sense-appetites; do not pander to the fickle mind; do not over-burden the senses and the understanding; do not over-procrastinate".

"Do not give way to anger and joy; do not nurse your sorrows; be not arrogant in success and dejected in defeat; remind yourself constantly of the vanity of things; be decided as to causes and their effects and consequently devoted to benevolent enterprises; do not grow complacent with your achievements; do not lose heart; do not recall calumny".

"Be devoted to *brahmacharya,* knowledge, charity, friendliness, kindness, joy, impartiality and peace".

Self-discipline

Discipline has been defined as training in proper conduct and action. As a verb, discipline means to educate, to train, especially to bring

under control. Discipline is a complex set of attitudes, behaviours, formal or informal instruction, rewards and punishment, which serve not to inhibit, restrict, subjugate or repress children but help them internalize appropriate cognitive processes, ideas and values; with these they will be able to ultimately exercise their own judgement and choose their own behaviour in ways best adapted to their situation. The wisdom of Ayurveda lies in incorporating a code of conduct in the Science of Life, as a means to ensuring mental health and happiness.

Chapter 14

HEALTH-RELATED BEHAVIOUR

1. ALCOHOL IN AYURVEDA & MODERN MEDICINE

Introduction

It is difficult to say if it was a fortunate or unfortunate accident when man first discovered that the juice of grape, if allowed to ferment, becomes wine. Alcoholic beverages have been used since the dawn of history. Charaka has praised wine as "the destroyer of sorrow, unhappiness, fear and distress". In addition to its beneficial effects as an appetite stimulant, tonic, tranquillizer and anaesthetic, wine was used by the ancient physicians as a vehicle for active therapeutic agents derived from plants. When the Arabs introduced the then new science of distillation into Europe in the middle ages, the alchemists believed that alcohol was the long sought elixir of life. Alcohol was therefore held to be a remedy for practically all diseases as indicated by the term "Whisky" which in Gaelic means "water of life".

Intemperance in the use of alcohol creates many problems — psychological, medical and sociological. All over the world one can witness the immense toll attributable to over-use of alcoholic drinks, in terms of illness, disability and death, decreased productivity, accidents, crime, family disruption and economic and psychologic hardship in all classes of society. It is impossible to quantify human misery and human suffering, but the havoc wrought by alcohol is underestimated rather than overestimated.

Effects of Alcoholic Drinks

The pleasurable as well as the harmful effects of alcohol have been known since antiquity.

Charaka Samhita contains a most balanced and objective evaluation of the merits and demerits of alcohol, which appeals to the contemporary reader.

"Wine is prepared from various substances and possesses various qualities. It has various actions on the body. It is intoxicating in nature. Hence it should be viewed from the point of both its good as well as evil effects".

"If a person takes it in right manner, in right dose, in right time and along with wholesome food, in keeping with his vitality and with a cheerful mind, to him wine is like ambrosia".

"While to a person who drinks whatever kind comes in hand to him, and whenever he gets an opportunity and whose body is dry due to constant exertion, that very wine acts as a poison."

"In the first stage of intoxication, the mind becomes stimulated. In the second stage the vital essence is slightly affected and in the third stage, it is completely affected".

"When the brain is affected by the action of alcohol there will result exhilaration, ardent desire, exultation, sense of happiness and various kinds of changes according to the psychic make up of the person and according to its *Rajasic* or *Tamasic* qualities. It promotes sound sleep and happy awakening. This is the first and happy stage of alcoholic effects."

"Fitful recollection, fitful forgetfulness, indistinct, thick and laryngeal speech, indiscriminate talk, unsteady gait, impropriety in sitting, drinking, eating and conversation—these are to be known as the symptoms of the second stage of alcoholic effects".

"After transcending the second stage and before reaching the last stage, there is no impropriety which persons of the *Rajasic* or *Tamasic* nature will not commit".

"Which wise man would ever wish to be intoxicated to an extent which is as frightful as insanity, even as no traveller would select a road which leads to an unhappy end and which is beset with many troubles?"

"Having reached the third stage of intoxication, he becomes paralysed like a felled tree, with his mind submerged in intoxication and stupor, and though alive, he resembles a dead man".

"He does not discriminate between, or recognize the qualities of things or his friends. He does not possess even a sense of his own happiness for the very sake of which alcohol is drunk".

"Which wise man would like to attain that state in which he cannot discriminate between what ought to be done and what ought not to be

done, between pleasure and pain, and between what is good and what is evil in the world?"

"On account of his addiction, he is condemned and censured by all people and is regarded an unworthy man by them. He gradually develops painful diseases as a result of his addiction."

"For all men, all that which contributes to well-being in this life and in the other, and happiness in that higher life of liberation, is established in the perfect tranquility of the mind".

"Wine causes great agitation to such a tranquil mind, like the strong wind that shakes the trees on the bank".

"Ignorant men, who are addicted to and are blinded by intoxication and overcome by passion and ignorance, consider the intoxicated state which is a greatly morbid and diseased condition, to be a state of happiness. These men, enslaved and blinded by alcoholism, are deprived of wisdom and 'Satvic' qualities and are lost to all goodness".

"Wine is also the cause of great delusion, fear, grief, anger and death as well as of insanity, toxicosis, fainting, epilepsy and convulsions".

"When a man is deprived of his very memory, then everything that follows upon it, is necessarily evil. Thus those who know the evils of drink, condemn the drink habit strongly. True and undoubted indeed are these great evil effects described about wine, if it is taken in excess or taken in disregard of the prescribed regulations".

"Wine by nature is regarded as similar to food in its effects. It is productive of disease if taken in improper manner, but is like ambrosia if taken in proper manner. Even food, which is the life of living creatures, if taken in improper manner, destroys life, while poison, which by nature is destructive of life, if taken in proper manner, acts as an elixir."

Merits of Measured Drinking

"Wine taken in proper manner soon induces exhilaration, courage, delight, strength, health, great manliness and joyous intoxication. It is an appetiser, digestive stimulant, cordial, promoter of voice and complexion, and is nourishing, roborant and strengthening. It relieves fear, grief and fatigue. It acts as a soporific to those suffering from insomnia and as a stimulant of speech in reticent people. It renders the mind unconscious of the pain of trauma, ligature and other kinds of pain and suffering. It increases the enjoyment of sense-pleasures and

the desire for the continuance of such pleasures. Even to the very aged, alcohol gives elation and delight. There is nothing comparable on earth to the delight derived during the first stage of alcoholic effects".

"The wise man who abstains from all kinds of intoxicating drink and who has his senses under control is not afflicted with any disorder due to alcohol, either somatic or psychic."

Proper Company at Drinking

"The men of excellent character, those that are pleasant of speech, that are amiable in expression, that are applauded by the good, that are versed in the arts, that are clean of heart and quick in the grasp of things, those that are mutually helpful and whose coming together is out of sincere friendship, who enhance the pleasure of drinking by their joy, affection and sweetness of manner and the sight of whom causes mutual increase of joyous spirits, such men indeed make happy companions at drink, for by drinking in their company, one enjoys delight".

Pharmacology & Metabolism of Alcohol

Ethyl alcohol or ethanol is the active ingredient in beer, wine, whisky, gin, brandy and other less common alcoholic beverages. In addition, the stronger spirits contain enanthic ethers, which give the flavour but have no important pharmacologic properties.

Alcohol is absorbed unaltered from the stomach and the small intestine. Its presence may be detected in the blood within five minutes after ingestion, and the maximum concentration is reached in 30 to 90 minutes. The ingestion of milk and fatty foods impedes the absorption of alcohol and water facilitates it.

After entering the blood stream, alcohol enters the various organs of the body, as well as the cerebrospinal fluid, urine and pulmonary alveolar air, in concentrations which bear a constant relationship to that in the blood. It is eliminated chiefly by oxidation to carbon dioxide less than 10 per cent being excreted chemically unchanged in the urine, sweat and breath. The energy liberated by the oxidation of alcohol is equivalent to 7 KCal/g.

The metabolism of alcohol takes place mainly in the liver, where several enzyme systems can independently oxidize alcohol to acetaldehyde. The most important of the enzymes is alcohol dehydrogenase. Another enzyme acetaldehyde dehydrogenase converts

acetaldehyde to acetyl co-enzyme A and acetate, and the latter are metabolized further through well-established pathways to yield carbon dioxide and water.

Ethyl alcohol is oxidized at a constant rate independent of its blood concentration; about 1 oz 90 proof whisky or 10-12 oz beer per hour. Chronic alcoholics metabolize alcohol somewhat faster than normal individuals. Amino-acids, especially alanine, insulin & fructose enhance ethanol metabolism. It is interesting to note that Charaka recommends "to eat, while drinking, salted fragrant flesh and fried flesh of many kinds of creatures of the land, water and air".

A scale relating to the various degrees of clinical intoxication to the blood alcohol levels in non-habituated persons has been constructed by Miles. At blood alcohol levels of 30 mg/dl (0.03 per cent) a mild euphoria is detectable, and at 50 mg/dl, a mild inco-ordination. At 100 mg/dl ataxia is obvious. At 200 mg/dl the subjects are drowsy and confused. At 300 mg/dl they are stuporous; a level of 400 mg/dl is accompanied by deep anaesthesia and may prove fatal. Such a scale has little pertinence to the chronic alcoholic patient whose liver increases the alcohol metabolic rate and who has developed tolerance to alcohol.

If the alcohol concentration in the blood is raised very slowly, few symptoms appear even at quite high levels. On the contrary, when the blood alcohol level peaks rapidly, the degree of intoxication is severe.

The most important action of alcohol is on the nervous system. It is not a stimulant, but a depressant of the central nervous system. The hyperactivity that is seen is due to removal of the inhibitory effects of the highest brain centres. The first functions to be lost are the finer grades of judgement, reflection, observation and attention, the faculties largely acquired through education which constitute the elements of restraint and prudence that man usually imposes on his action.

There is a common belief that alcohol is an aphrodisiac, but the reality is very well expressed by William Shakespeare, "It provokes the desire but it takes away the performance." Performance in other forms of athletics is also impaired by alcohol, hence managers of cricket teams are wise to keep a close vigil on this score.

In general, efficiency, both mental and physical, is reduced by alcohol in any amounts worth taking for social purposes. There is an important exception; the person, who is so disabled by anxiety or nervous tension that his performance is gravely impaired, may improve with the correct dose of alcohol.

The effects of alcohol become of crucial importance in case of pilots or car or truck drivers. In Britain, a blood concentration exceeding 80 mg alcohol per 100 ml blood while in charge of a car is a statutory offence. At this concentration the liability to accident is twice normal. Other countries set other concentration limits, some lower, some higher, but even for experienced professional drivers there is no "safe" blood alcohol level below which it is certain that judgement would not be impaired. The danger remains even after alcohol has left the blood, during the hang-over period, due to irritability, fatigue or hypoglycaemia (low blood sugar). All-over the world the adolescents and adults who drive after drinking are a grave menace to public safety.

Causation of Alcoholism

Alcoholism has been defined both as a chronic disease and a disorder of behaviour, characterized in either context by drinking of alcohol to an extent that interferes with the drinker's health, interpersonal relationship and/or means of earning a livelihood. In pharmacological terms, it is addiction to alcohol.

The important question is why individuals drink excessively, often with full knowledge that such action will result in physical injury to themselves and irreparable harm to their families.

There is probably a genetic influence in the development of alcoholism. It has been shown that the concordance rate for alcoholism in identical twins is 55 per cent or higher and for fraternal twins of the same sex, 28 per cent. The incidence of alcoholism is 4 to 5 times higher in the biological offsprings of alcoholic parents. Thus, it appears that genetic factors are important, in addition to psychological and social and cultural ones.

Alcoholism should be taken as a symptom or manifestation of maladaptation to many social or environmental stresses or psychological difficulties which the person has been unable to handle. Psychological characteristics associated with alcoholism may provide useful clues for management. These include a low frustration threshold, excessive dependency needs, underlying feeling of inferiority, inadequacy or self-doubt. Many alcoholics are sensitive to rejection and have difficulty in entering into close social relationships. They may reveal recurrent themes of depression, emptiness and loneliness. Alcoholism is commonly rooted in family and marital problems, which may need help by specialised agencies like marriage counsellors.

Very often it is not the patient but the wife or close relatives who can see more clearly how seriously his life is being interfered with by his alcoholic addiction. These unwilling patients are particularly difficult to treat. But the prospect is very different when the patient himself is distressed by his dependence on alcohol and is anxious for a change.

The problem of excessive drinking is formidable but not necessarily hopeless. A useful point at which to undertake this task is during convalescence from a serious medical or neurological complication of alcoholism or in relation to loss of employment, arrest or threatened divorce. Such crisis may help convince the patient, better than any argument presented by the family or physician, that the drinking problem has reached serious proportions.

The following is a list of alcohol-induced diseases with which the patient may present himself.

Alcohol-induced Diseases:

Gastrointestinal System

Alcoholic gastritis—morning nausea & vomiting.
Peptic ulcer (higher incidence).
Mallory-Weiss Syndrome (due to persistent vomiting).

Liver

Fatty liver (reversible on abstinence).
Alcoholic hepatitis.
Alcoholic cirrhosis.
Hepatic coma.
Chronic hepatocerebral degeneration.

Pancreas

Pancreatitis.
Steatorrhoea due to deficient exocrine pancreatic function.

Haemopoietic System

Bone marrow depression.
Anaemia with macrocytosis.
Leucopenia.
Thrombocytopenia.

Nervous System

Alcohol intoxication
Withdrawal syndrome—delirium tremens
Nutritional deficiency secondary to alcoholism:

a. Wernicke-Korsakoff syndrome
b. Polyneuropathy
c. Cerebellar degeneration
d. Optic neuropathy
e. Pellagra.

Uncertain pathogenesis, associated with alcoholism:

a. pontine and extrapontine myelinolysis
b. Marchiafava-Bignami disease
c. alcoholic dementia
d. alcoholic central atrophy
e. fetal alcohol syndrome

Cardiac & Skeletal Muscle

Alcoholic cardiomyopathy
Alcoholic myopathy

Ayurvedic Treatment of Alcoholism

The prescription for the "Vata type" of alcoholism (hiccup, dyspnoea, tremors, insomnia, excessive garrulity) makes interesting reading. "Various kinds of confections and various appetisers, meat preparations, dry massage, hot baths, affectionate embraces of women's bodies full of the warmth of youth, by the arm clasp of their waists, thighs, and full-grown breasts, by the warmth of the bed and the cover and the warmth of happiness and cheer of the interior apartments subdue alcoholism by the vata type"

The same therapy is recommended for two complications of alcoholism called "Dhwamsaka".

Modern Treatment of Alcoholic Addiction

The requisite for successful treatment is total abstinence from alcohol, and this represents the only permanent solution.

The doctor, the therapeutic team, the family and friends have to accept the alcoholic as a sick person needing help. It does not help to adopt a sermonising, moralising, judging or condemning attitude towards him. A rigid and punitive attitude may be counterproductive. The physician, family and friends should enhance motivation not to

drink by caring about what happens to him, being reasonably optimistic about the outcome, showing him feasible ways to begin to deal with his problems rather than evade them or drown them in alcohol. Helping the patient to explore his capacity for alternative modes of adaptation to his life situations and to arouse and to develop the patient's own adaptive potentialities will be necessary. It is worthwhile assuming that the patient would not be alcoholic if such alternatives were easily available and readily apparent to him.

Alcoholism has to be considered essentially a relapsing disorder. A relapse is to be taken as a challenge to try again and not to throw up arms because of a feeling of personal failure or affront. No treatment can succeed with an alcoholic without his motivation and cooperation. Treatment of alcoholic addiction initially consists of "drying out" which often calls for hospital admission. Sudden withdrawal of a sustained high uptake of alcohol may result in the onset of delirium tremens, characterised by gross tremors of the hands, great restlessness, misidentification of persons and places, and delusional ideas which may be terrifying—these withdrawal symptoms can be well controlled by drugs like phenothiazines, diazepam, haloperidol or chlormethiazol. The next phase of treatment once the patient is abstinent is to explore with him by means of a series of interviews his personal and other problems which require attention. The abstinent alcoholic can ensure against the temptation of another drink by taking "antabuse" drugs like disulfiram or citrate calcium carbimide. When on those drugs, the patient will have a very unpleasant reaction after taking even a small amount of alcohol. Metronidazole, a drug commonly used to treat amoebic infections, and oral antidiabetic drugs, also cause a similar antabuse effect.

Disulfiram interferes with the metabolism of alcohol so that patients who take both alcohol and disulfiram accumulate an inordinate amount of acetaldehyde in the tissues, resulting in nausea, vomiting, hypotension. The experience is so nasty that the patient does not like to repeat it. The patient taking disulfiram, aware of the danger of mixing liquor and the drug, is protected against the impulse to drink, and this protection may be renewed every 24 hours by the simple expedient of taking a pill. Compliance can be checked by measuring disulfiram levels in the blood. The willingness with which the patient accepts this form of treatment is an index of his motivation.

Alcoholics Anonymous (AA), a world-wide movement (including India) whose members are ex-alcoholics, is a great help in rehabilitation

of alcoholic patients. Group discussions help patients to gain insights into their problems and personality difficulties, so that they learn to cope with inner tensions and environmental stresses in a more mature and less destructive manner than by seeking oblivion in alcohol.

2. TOBACCO SMOKING AND HEALTH

Introduction

Charaka Samhita contains a detailed discussion on medicinal smoking. Medicinal smoking can be defined as inhaling smoke of medicines through the nose or the mouth. Smoking of tobacco or ganja (hash hash) should not be considered as medicinal smoking, since there are no medicinal benefits.

Charaka classifies smoking according to its uses, under:

(A) *"Prayogika":* It is advised for regular use by persons of "sama" and "kapha" constitution. The medicines commonly used — harenuka, priyangu, pruthvika, keshar and naka.

(B) *"Snigdha":* Smoking with oily medicines such as ghee, wax, animal fat, jeevaka and rhushabhaka.

(C) *"Vairechanika":* Smoking of strong types used for its cleansing action on air passages. Medicines commonly used are shveta, jyotismati, haritala, manashila, and leaves of agaru, turmeric and castor roots.

(D) *"Kasaghna":* Smoking to relieve cough, with medicines like glycerrhiza, ajamoda, jeevanti, agaru, sarjaka, roots of castor plants, vacha, asafoetida, bhurja granthi, and ghee prepared on silk cloth.

For patients with asthma, a *"Shvasaghna"* smoking is prescribed with various ingredients.

For patients with ulcers in the mouth, pharynx, trachea and air passages, a *"Vranadhoopana"* smoking is prescribed, using java, shriveshtaka, sarja rasa and ghee.

A medicated cigarette is prepared from grass sticks and put in a smoking tube or pipe, the dimensions of which are prescribed according to the types of smoking as described earlier.

Charaka gives a list of persons in whom smoking is contraindicated, such as children under the age of 18, pregnant women, persons with head injuries, eye diseases etc.

Various benefits of medicinal smoking are claimed, I am not aware of any scientific studies to validate those claims. Moreover, medicinal

smoking does not appear to be widely employed by Ayurvedic practitioners.

Tobacco Smoking

Tobacco smoking and its ill effects are not mentioned in Ayurveda. It is not clear when the practice of tobacco smoking was started in India. Tobacco smoking is perhaps the world's most accepted vice. Those who have never smoked a cigarette in their life may consider the topic of smoking, with its alleged pleasures, addiction and miseries, with a sense of calm detachment. Recent research has revealed that non-smokers in a smoky atmosphere are also prone to disease as much as the smokers, which makes the smokers' an enviable lot — they get both the pleasure and the cancer while the non-smokers may get only the cancer! How do people start smoking? When you are young you take to your first cigarette imitating others — mainly because your friends are smoking and you feel a bit left out — or you want to prove your manhood or grownupness. Although the initial experience is often quite unpleasant, many continue to smoke for self-esteem or status need. The films or advertisements show every smoker as a handsome, young, healthy, wealthy and relaxed man with a pretty girl admiringly watching him light his cigarette, hence the impressionable youth identify smoking with manhood, success and happiness.

Psychoanalysts suggest that getting something orally is the first great libidinous experience in life; first the breast, then the bottle, then the comforter, then food and finally the cigarette. The common sight of a pipe smoker with an empty or unlit pipe in his mouth would seem to lend support to this.

The reasons people habitually smoke tobacco are certainly complex and it is no easy matter to reach a simple and reasonable conclusion concerning the mental health aspects of smoking. Some people smoke purely for pleasure when resting, reading or watching television. Others smoke out of sheer boredom. For some it reduces fatigue in monotonous or demanding tasks. Most people smoke more when under tension because they find that smoking relieves their tensions. There is no clear-cut personality difference between smokers and non-smokers. Cigarette smokers tend to be more extroverted, less rigid and perhaps more neurotic than non-smokers. Pipe smokers are notably introverted.

Social environment plays a large part in determining smoking, and the offering and acceptance of cigarettes is important in the development of

personl relations in business and in private life. What is it that gives satisfaction to the tobacco smoker?

Action of Nicotine

The sole physiologically active ingredient of tobacco smoke is nicotine. Although cigar and pipe tobacco contain considerably larger quantities of nicotine than does cigarette tobacco, their heavy alkaline smoke is intensely irritating to the respiratory tract and is not usually inhaled. On the other hand, the light, bland smokey cigarette with practice, is readily tolerated by the bronchial tree. Accordingly, nicotine is rapidly and completely absorbed in the lungs of the cigarette smoker.

The novice smoker commonly experiences the toxic effects of nicotine; giddiness, nausea and vomiting, abdominal cramps, cold sweat and even collapse with a fall of blood pressure. These symptoms, when unusually severe, may deter formation of the smoking habit. The veteran smoker does not acquire tolerance to nicotine, inasmuch as all measurable circulatory responses persist without attenuation, but he learns to manipulate time-dosage factors so as to avoid poisonous effect.

A standard cigarette contains about 20 mg. nicotine. Considerable amounts of nicotine are destroyed by heat or dispersed in the side-stream smoke, so that the average inhaling cigarette smoker absorbs about 2 mg. of nicotine. This amount causes small but consistent increases in heart rate, in systolic and diastolic blood pressure, in the work of the heart. Blood flow to the skin and temperature of the skin are sharply reduced. All these effects are similar to those produced by the hormones adrenaline and noradrenaline, and in fact in human subject the urinary excretion of adrenaline metabolites may increase upto 50 per cent after heavy cigarette smoking. Adrenaline and noradrenaline are the body's emergency hormones, produced by strong emotions like sudden rage or fear and prepare the body for fight or flight. The heart rate speeds up, the arteries tighten to raise blood pressure, digestion comes to a halt, and sugar from the liver and free fatty acids from the fat stores are mobilized into the blood stream to provide more fuel for the muscles. Platelet stickiness is enhanced and clotting capability of blood is quickened, in case of injury. By smoking continuously the smoker is perpetuating this state of emergency, which nature designed only for short periods of time. The price paid for this artificial thrill of 'living dangerously' is in the form of heart attacks. Smoking twenty cigarettes or more daily is associated with a

hazard of heart attack three times greater than in non-smokers or in cigar or pipe smokers. Angina pectoris or chest pain due to less blood supply to the heart, is often precipitated or aggravated by smoking, suggesting that the effects of cigarette smoking are acute as well as chronic. Cigarette smoking makes the heart patient more liable to a dangerous and life-threatening complication, namely ventricular fibrillation.

Action of Other Ingredients

Apart from nicotine, it seems increasingly probable that carbon monoxide is the chief toxic constituent of cigarette smoke in relation to cardiovascular complications. Heavy cigarette smokers have carboxy haemoglobin concentrations of 2-15 per cent. Even at low levels, carbon monoxide causes hindrance to the smooth transfer of oxygen from the oxygen-carrying red blood cells to the tissues where it is needed. Normally this is achieved by the red pigment oxy-haemoglobin which transfers oxygen readily. Carboxy Hb does not give up its oxygen readily. This is a particularly serious handicap to the patient whose coronary arteries are already narrowed, hence his increased oxygen requirements on exertion cannot be met by increase in blood flow.

When carboxy haemoglobin reaches 20 per cent it inhibits oxygen utilisation by cells of the vessel walls and favours the formation of atheroma, or thickening of arteries.

Cigarette smoking harms the heart patient in yet another way. The normal air passage is lined by cells with microscopic hair or cilia which wave to and fro like wheat in the wind, about 12 times a second. Their upward thrust does an important cleaning job by bringing up trapped dust particles in sticky mucus. Cigarette smoke or badly contaminated air paralyse the cilia; if the irritation continues the cilia wither and die, never to be replaced. Now the only mechanism left for cleaning the airway is the noisy, inefficient smoker's cough which has replaced the quiet efficiency of the cilia. Cigarette smoking is the most important cause of chronic bronchitis and is significantly related to another lung disease namely emphysema. Both bronchitis and emphysema aggravate heart disease of any type.

Smoking should be prohibited for the heart patient. The patient with angina pectoris should not smoke. A well-known cardiac surgeon said recently that he refuses to do coronary bypass surgery on any patient who refuses to stop smoking. "If a man thinks smoking is more important to him than his heart, then I will have nothing to do with him".

The simultaneous presence of several risk factors is more than merely additive. If the patient is a male, above 45 years of age, has a blood cholesterol level over 250 mg. per 100 ml, has a diastolic blood pressure over 90 mm Hg, is overweight and is a smoker, his risk of a heart attack is 44% as against 9% if none of these factors were present.

Almost all patients of Buerger's disease (thromboangiitis obliterans) are male tobacco smokers. If the patient stops smoking completely, arrest of the disease is usual. If he continues to smoke, progression of this disease is almost a certainty.

If the cigar and pipe smokers, after reading this tirade against cigarettes, are getting a feeling of security and comfort about their choice, there is bad news for them. Excessive smoking of strong pipe tobacco may cause damage to the nerve of the eye-optic neuritis. Tobacco smoke contains cyanide which experimentally has been shown to cause demyelination. Hydroxycobalamin, derived from Vitamin B12 plays an important part in the detoxication of cyanide. If the intake of Vitamin B12 is low and cyanide ingestion is high, demyelination of the optic nerve is likely to occur. A typical history is that there is a growing inability to see colours of small objects. A mist obscures the central field of vision and gradually becomes so intense that it becomes impossible to recognize acquaintances. There is usually no pain.

Smoking and Lung Cancer

The most dreaded and most publicised complication of cigarette smoking is of course lung cancer. In the 1940's there was a growing impression that environmental factors are responsible for most human cancers and a relationship between cigarette smoking and bronchogenic cancer emerged as an important link. Doll and Hill in England in 1951 chose doctors on the medical register in Britain and asked them to record their smoking habits at that time. They then recorded the deaths that occurred in the next few years and calculated the death rates from lung cancer. Their results were very striking indeed: as against 7 deaths per 100,000 in non-smokers, there were 47 in light smokers, 86 in moderate smokers and 166 in heavy smokers. Doctors are a particularly suitable population for prospective study because they are comparatively easy to follow up and when sick, usually choose leading physicians to care for them. Their death certificates are therefore more than usually reliable. Hence the conclusion, based on the study of almost 60,000 doctors in England, can be accepted that heavy smokers (more than 20

cigarettes per day) have death rates from lung cancer 23 times greater than non-smokers.

The tar component of cigarette smoke contains a cancer producing chemical called benzopyrene. It is also likely that alpha radiation is another contributing factor in tobacco-related cancer. The alpha emitters, polonium-210 and lead 210 are highly concentrated in tobacco trichomes. The major source of polonium is phosphate fertilizer which is used in growing tobacco. In a person smoking 30 cigarettes a day the radiation dose to the lining of the airway is 8000 millirontgens per year. The alpha particles have a high mutagenic potential.

It must be appreciated that environmental factors alone cannot explain the range of susceptibility of individuals in a population exposed to the same or similar carcinogenic agents. Clearly genetic influences are at work. But since genetic factors are beyond our control, we concentrate on what can be controlled. In the United States of America, there is a group called Seventh Day Adventists, whose religious faith prohibits smoking. They have 1/8 incidence of lung cancer compared to the non-members. In respect of cancer of other body sites there is no difference between the groups, so that the Seventh Day Adventists have evidently no genetic immunity from cancer.

The "bidi" is a typical Indian product consisting of strong powdered tobacco wrapped in dried "tendu" leaf grown extensively in Andhra Pradesh and Orissa. It is essentially a poor man's smoke, and an estimated 100 million bidies are smoked daily in India. Out of every eleven Indian smokers, ten are bidi smokers.

When the cigarette smoking public in the Western Countries were warned about the harmful effects of cigarette smoking, a large number turned to bidi smoking in the belief that it was less harmful than cigarettes. A comparative chemical analysis of Indian Bidi and American Cigarette smoke was published a few years back in the International Journal of Cancer. A single bidi delivers about one-and-a half times the carcinogenic hydrocarbons delivered by a single cigarette. Phenol, a cancer promoting agent, is also found in larger amounts in bidi smoke than in cigarette smoke. Thus the bidi, if any thing, is more dangerous.

Since the appearance of the Surgeon General's report in U.S.A. in 1964, there have been marked changes in the cigarette smoking habits of Americans. By 1975, the proportion of men smoking cigarettes had declined by 25 per cent, from 53 per cent in 1964 to 39 per cent in

1975. There has been increased use of filter-tip cigarettes which contain less tobacco than regular cigarettes.

Recently, the Ministry of Health in New Delhi wrote to State Governments about getting the health warning printed on bidi bundles. Some states have expressed doubt about the effectiveness of this action, for a large number of bidi smokers are illiterate. Besides, experience all over the world has shown that the statutory health warnings on cigarette packs have been of little help in dissuading people from smoking, especially women and teenagers.

Women have taken to smoking in Western cultures in larger numbers than ever before and they have also started paying the price for it. Women who smoke during pregnancy have a higher incidence of abortion, babies 170 gm. lighter and a fetal and neonatal mortality rate 28 per cent higher than non-smokers and retarded, later development of the babies. Facial wrinkles above age 30 years correlate with the number of cigarettes smoked.

Benefits of Stopping Smoking

Despite all the knowledge about the harmful effects of tobacco smoking, health education, and the statutory warning about harmful effects of smoking, the sales of cigarettes have increased in the past few years. What are the reasons? Many smokers believe that after some years of smoking it is useless to give up because the damage is done already. This is not true. Stopping has been shown to reduce the mortality from lung cancer as well as from sudden cardiac deaths. Abstention from cigarettes may improve longevity, since morbidity data indicate that former cigarette smokers are at little if any greater risk than non-smokers, for cardiac deaths. Stopping smoking accelerates the healing of gastric ulcers. Stopping smoking completely arrests the progress of the peripheral vascular narrowing in Buerger's disease.

The primary motivation for giving up smoking is the risk of ill health and death. Many people do in fact give up smoking following a heart attack. But prevention must start much earlier. Less than 20 per cent of smokers become non-smokers at present.

According to Mark Twain it is very easy to stop smoking. "I ought to know", he said, "because I have stopped smoking a thousand times!"

For the moderate smokers (less than 20 cigarettes per day) who really are motivated to give up smoking and who cannot do it in a single

shot, here are some ways to begin "Nicking the habit".

1. Choose a cigarette with less tar and nicotine.
2. Smoke only the first half of the cigarette.
3. Reduce the number of times a puff is taken.
4. Reduce the depth of inhalation.
5. Smoke fewer than 3 cigarettes a day.
6. Exercise more.
7. Pursue other hobbies and interests.
8. Find a safe substitute for handling cigarettes like a lucky coin, pen or pencil.

The list of tips to stop smoking is endless and challenges the creative ability of the doctor to adapt and personalise the patient's management. People who smoke more than 20 cigarettes a day are exceedingly more difficult to motivate. Stronger encouragement, guidance and support are required. Anti-smoking group sessions, on the lines of Alcoholics Anonymous, may prove to be of added value. The health and life of patients is the first concern of the doctor. The World Health Organisation in 1970 condemned the use of tobacco smoking on account of its consequences for health. The medical profession should therefore be in the forefront in the efforts to persuade their patients to adopt a more healthy way of life, to dissuade the young from beginning to smoke and to persuade the smoker to stop smoking.

3. PSYCHOTROPIC DRUGS

Introduction

In earlier sections I discussed the health hazards of alcohol and tobacco smoking. Western society is presently concerned greatly with the use and misuse of psychotropic and recreational drugs particularly by the younger generation. Society has accepted alcohol and tobacco smoking as "legal" while the psychotropic drugs are considered "illegal". Far too often the legal drugs alcohol and tobacco are treated as if they are much safer than, and altogether different from, illegal drugs. Scientific opinion stresses the common ground between the two; many different types of drug-related behaviour can be considered in general terms. The evidence about why people use drugs and what happens to those people, is strikingly similar in relation to both legal and illegal drugs. In addition, ideas about what constitutes addiction or drug dependence, and conclusions about what becomes of dependent individuals also appear similar in relation to legal and illegal drugs. It is

very essential that society develops a proper perspective.

Drug use in some form or other is virtually universal. From time immemorial, people have sought a change of consciousness with the aid of whatever appropriate vegetation or other source was available. Alcohol, man's oldest drug, is the most widely used because it can be produced from the fermentation of so many types of plant products.

Great Social Problem:

During the 20th Century "drug misuse" has become widely regarded as one of the world's great social problems. The complexity of the situation has been perceptively described by Professor Griffith Edwards:

"If you fly over any part of the earth's land surface, you would have a fair chance of seeing below you some process of drug cultivation. You would see vineyards, coffee plantations, tea plantations, tobacco crops, fields of opium poppy and patches of lank Indian hemp flowering even on vacant city lots: the coca plant grows on the slopes of the Andes, so that six million peasants shall obtain their cocaine. Even the desert has the peyote cactus. As you look down on the great industrial countries, the factories will catch your attention, which spill out the tranquillizers, stimulants, analgesics, sedatives and antidepressants, by the billions, and the chemist much improves on cactus and mushroom. The money at stake is immense and countries might fill their treasuries to a large extent from drug revenues. Conflicts of opinion are violent, the state's response to impermitted use Draconian."

Popular Misconceptions

Public thinking about the drug problem is highly coloured by lurid media coverage which has often exaggerated and sensationalised both the scale and meaning of various forms of drug abuse. A great deal of propaganda is designed to frighten people away from experimenting with illegal substances such as Cannabis indica ("bhang", "charas", "ganja"). Society generally acknowledges that drinkers vary enormously and that most do not appear to suffer from ill effects as a result of their alcohol consumption. Similar conclusions are as valid for cannabis. Those who panic about smoking "grass", conveniently forget that 25,000 people are dying each year in Britain alone from the direct effects of tobacco smoking and that over 226,000 drunkenness convictions, 18,000 hospital admissions for alcoholism occur in that country

every year. And yet an energetic vendor of alcohol or tobacco, especially an exporter of these things, might justifiably expect his efforts to be rewarded by a State Award, while an energetic trader in Cannabis will be lucky to escape a long prison sentence. This is the paradox in an intelligent society.

Like alcohol any psychotropic drug is likely to be used unwisely, harmfully and excessively by some people. The more widely a drug is used, the greater is the risk of some form of harm or misuse in relation to it.

Effects of Psychotropic Drugs: Cannabis

Cannabis (marijuana), derived from the plant *Cannabis sativa,* occurs in two varieties, the hemp type and the drug type. These differ in relation to the amount of the main psychoactive ingredient, delta 9-tetrahydro cannabinol (THC) that they contain. The hemp type (used for rope making) contains relatively little of the intoxicating substance, while the drug type contains far greater levels of THC. Cannabis has been used for thousands of years, in China, India, and subsequently in Middle East and North Africa. Cannabis was adopted by Western Medical Practice during the 19th Century. The introduction of much more effective and useful drugs has long since removed the use of cannabis from medical practice. Its use on a large scale has been for recreational purposes by Western Youth.

Marijuana consists of the flowering and fruiting tops and leaves of the plant. Very often seeds, stems and other parts of the plant are also included.

Cannabis resin (hashish, Charas) is the dried caked resin derived from the tops and leaves of the female plant. Because of its higher THC content it is more potent than marijuana.

Cannabis oil, a ruddy brown extract from the resin or the plant, is known by a variety of names, including "hash oil" or "liquid hash". This is the most potent form of cannabis apart from pure THC. Hash Oil may contain a THC concentration of 25 to 60 per cent. Cannabis is normally smoked, although it may also be chewed or ingested as an ingredient in food or drinks. A typical marijuana cigarette contains 0.5 to 1 g. of plant material.

Cannabis, like alcohol, is a depressant drug on the central nervous system, slows reaction time, impairs co-ordination and may induce drowsiness. The desired short-term reaction is a "high" or euphoria

similar to mild alcoholic intoxication. This may be followed by a quieter, passive phase which in turn is followed by sleep. Reddened eyes and increased pulse rate are also common-place, short-term effects. Experienced users report that they achieve the greatest effects by inhaling the smoke and holding it in their lungs.

Tolerance may develop very rapidly with cannabis, so that users sometimes need to smoke steadily increasing amounts to recapture the original effects of the drug. THC potentiates with alcohol, amphetamine and tobacco. Consequently, their combined use magnifies the effects. Some cannabis users certainly become psychologically dependent on the drug. Derivatives of cannabis accumulate in the tissues of the brain, lungs and the sex glands. Prolonged and heavy cannabis use has been found to cause damage to the blood cells and spermatozoa. Animal studies have shown that cannabis use in pregnant mammals increases the incidence of fetal damage and death. There is abundant evidence to support the view that prolonged heavy cannabis use is physically damaging (particularly lung function) and is likely to lead to loss of motivation, apathy and passivity. To some extent the "amotivational syndrome" may be attributable to the ideology and life-style of the drug scene rather than the chemistry of cannabis.

Large numbers of cannabis smokers use the drug only intermittently and they do so without harm. Even so the potential dangers of the regular cannabis use make it a health hazard, like alcohol and tobacco smoking.

Lysergic Acid Diethylamide—LSD

LSD is possibly the most dramatic of the psychotropic drugs. Its characteristic effect is to distort the way its user sees and senses the world.

Many hallucinogenic drugs (sometimes called psychedelics) occur naturally and have long been used in South, Central and North America for recreational purposes or in conjunction with religious ceremonies. The substances include peyote (a cactus) and mescalin (a mushroom).

LSD is by far the most potent of the commonly available hallucinogens. It was first produced in 1938, and its hallucinogenic effects were noted in 1943 and since then it has been used experimentally in psychiatry, although its use for such purposes is now almost

non-existent. The subjective effects of LSD have been vividly described in Aldous Huxley's "The Doors of Perception". It has been hailed by some as mind-expanding, a key to self-enlightenment. LSD is an incredibly potent drug. Tiny amounts are sufficient to trigger off a "trip" or experience which may well be psychologically overwhelming and routinely lasts for as long as seven hours. The drug is available in many forms: capsules, microdots or as a liquid. It is usually prepared as a tartrate salt that is water-soluble. It is easily carried or smuggled and is often soaked in sugar or blotting paper. It is usually swallowed, but may also be sniffed or injected. The effects normally begin an hour or so after ingestion and reach their peak two to three hours later. The effects do not directly depend on dose and as little as 30 or 40 micrograms are sufficient to produce the desired effect. LSD accentuates and distorts the users' antecedent mental and emotional state. LSD often causes profound changes in perception and mood. These may be extremely pleasant or devastatingly horrifying. High blood pressure, rapid pulse rate, rapid respiration, nausea, weakness, convulsions and depression may also occur.

Flash-backs, or recurrences of the effects experienced during an LSD trip have been widely reported by users even months after experimentation. Sometimes such flash-backs occur at dangerous or at least embarrassing times.

There certainly have been fatal accidents and suicides attributable to LSD, although extremely rare. While LSD does sometimes produce extremely interesting and enjoyable effects, those cannot be relied upon and users participate in a hazardous game of Russian roulette.

Heroin & Other Opiates

The juice of the oriental poppy (papaver somniferum) has been used for pleasure and medical use for thousands of years. The practice of using opium for diarrhoea and for making children quiet was wide-spread all over the world till the 1920's.

Morphine, the active alkaloid of the opium poppy was isolated in the mid-nineteenth century, and since it was available as a solution for injection, became popular as a potent pain-killer. Heroin (diacetyl morphine) was derived in 1898, ironically, as a result of a quest for safer, less addictive morphine derivatives. Subsequently other similar drugs, synthetic or semisynthetic opiates have been produced. All have been shown to produce *drug-dependence and addiction.* The number of heroin

addicts in USA alone is estimated to be about 500,000. The cost to the nation, of heroin abuse alone is about six billion dollars a year.

Morphine and heroin are mainly injected, but may also be eaten, smoked or sniffed. All opiates produce tolerance if used regularly and abrupt cessation of regular use may produce withdrawal symptoms. Heroin withdrawal symptoms usually occur six to twelve hours after the last dose. They range from minor discomfort, similar to that from a cold, to cramps, nausea, sweating, dilated pupils, diarrhoea, headache and insomnia. Usually withdrawal passes its worst within two to three days and recovery generally takes no more than a week, although it often takes longer for sleep patterns to return to normal.

Heroin users often use syringes and needles which are unsterile, or share them with other users, thereby spreading viral hepatitis and syphilis. Sometimes heroin bought on the black market contains highly dangerous substances such as caustic soda added to increase the weight and thereby the vendor's profit.

Babies born to addicted females are also physically dependent and might die unelss this condition is detected and treated.

A number of factors, socio-economic, psychological and pharmacological, all contribute to the genesis of opium and heroin addiction. The most susceptible are young men or delinquent youths living in the economically depressed areas of large cities. Group pressure and peer pressure are very potent factors for initiation of addiction in the youth, mostly under age 21.

Cocaine

Cocaine is derived from the coca plant (Erythroxylon coca) which grows in South America, South-East Asia, Africa and the West Indies. Coca has been used for cènturies in South America as a cure for a variety of ailments such as rheumatism, and as a stimulant. The Incas regarded Coca as a divine plant with magical properties. The active alkaloid cocaine was isolated in the mid-nineteenth century, and it is far more powerful and potentially dangerous than the mild coca leaves which contain 1 to 1.5 per cent cocaine.

Cocaine is a stimulant and as such may be broadly compared with the amphetamines. Cocaine is a white crystalline powder, usually sniffed when used recreationally. The drug is rapidly absorbed from the nasal mucosa and produces a brief, dose-related stimulation and enhancement of mood. It induces alertness and energy. Sniffing

cocaine is a potentially very dangerous practice, which can erode through the septum of the nose.

Although it has been assumed that use of cocaine is relatively safe, death caused by respiratory depression and cardiovascular collapse has been documented after cocaine "snorting" (inhalation) and after intravenous administration. Protracted cocaine abuse may induce paranoid ideation and visual and auditory hallucinations.

Cocaine is very expensive in comparison to other illicit drugs and has attained the reputation of a "status" drug in western industrialised societies.

Amphetamines

Three categories of this group, amphetamine (benzedrine), dextro amphetamine (dexedrine) and methyl amphetamine (methedrine) have been widely available, and hence used recreationally on an unprecendented scale. Amphetamine misuse reached its peak in Japan where it was estimated that half a million people were using it non-medically in 1954. During the Viet Nam war American soldiers used 225 million amphetamine tablets. Amphetamines are stimulants which produce feelings of energy and confidence. They increase heart rate, blood pressure and blood sugar. The pupils are dilated and appetite is suppressed. They enable users to remain awake for longer periods. For these reasons they have been used illegally to stay awake at parties, dances and concerts, or simply to generate a feeling of energy and euphoria. In many ways the effects of amphetamines resemble those of adrenaline. Excessive amphetamine use has, rarely, led to fatalities due to burst blood vessels in the brain, and heart failure.

While the effects of moderate doses of amphetamine may be pleasant, its often produces restlessness, anxiety and overconfidence. Amphetamine does not create energy, it simply uses it up so that fatigue invariably follows stimulation, often combined with irregular sleep pattern. This is known as the amphetamine "crash".

Phencyclidine (PCP) "Angel Dust"

One of the nastiest and most dangerous substances to be used recreationally during recent years is "angel dust"—phencyclidine hydrochloride. This substance, also colloquially known as PCP, crystal, super grass, goon, scuffle etc. was first produced over twenty years ago as an anaesthetic. During the 1960's it was used by youthful

drug takers in USA and its excessive misuse has recently caused considerable public concern.

PCP is a hallucinogen. It is available either as "Angel Dust" in crystalline form, or may be easily dissolved in water, for ingestion or injection. The usual or desired effects of PCP are a "high" accompanied by a feeling of detachment, dreaminess or pleasant or exciting hallucinations. The effects may be dramatically unpleasant and may cause depression, panic and psychosis, and self-destructive behaviour. Thus PCP is a major health hazard.

Sedative-Hypnotic Drugs

The barbiturates, and the benzodiazepines are the most commonly prescribed sedative drugs today. More than 1.4 billion prescriptions for these drugs are filled each year.

Despite the steadily diminishing medical use of barbiturates (being displaced by benzodiazepines), the high incidence of addiction, suicides and accidental deaths attributable to the improper use of these drugs is a matter of continuing concern. The Domestic Council Drug Abuse Task Force (1975) in USA estimated the total number of regular users of barbiturates who were "in trouble" (suicidal and accidental overdoses and medical complications of barbiturate abuse) to be 300,000.

Chronic barbiturate addiction, like other addictions, tends to develop on a background of some psychiatric disorder, most commonly depression or psychoneurosis with symptoms of anxiety and insomnia.

As the desired effects of the drug are lost by continuous use (tolerance), the patient increases the dose gradually until he or she is taking an amount sufficient to produce symptoms when it is withdrawn. Alcoholics find that barbiturates effectively relieve their nervousness and tremor; then they may continue to take both alcohol and barbiturates. Heroin and morphine addicts may turn to barbiturates when they are unable to obtain opiates. As with other addicting drugs, the incidence of barbiturate addiction is particularly high in individuals with ready access to drugs such as doctors, nurses and pharmacists.

The benzodiazepines, librium and valium have been used extensively to control anxiety, and over-activity. While comparatively safe in the recommended doses, they are far from ideal. They frequently cause unsteadines of gait and drowsiness and at times hypotension and syncope, particularly in the elderly.

The carbonic acid derivatives, exemplified by meprobamate, have a modest sedative action and can relieve mild degrees of nervousness, anxiety and muscle tension. Addiction to meprobamate can occur, and if four or five times the daily recommended dose is taken over a period of weeks to months, withdrawal symptoms, including convulsions, may appear, resembling those which follow chronic barbiturate intoxication. There have been occasional reports of death following the withdrawal of meprobamate and diazepam in persons who had been taking large doses of these drugs for protracted periods. In view of these observations, extreme caution must be exercised in prescribing new sedative drugs which are continually being introduced and which are said to possess no addicting or habit-forming properties.

Why People Use Drugs?

Three general types of theories have been suggested to explain drug addiction. These are constitutional, individual and environmental.

Animal research has shown that sometimes there is a genetic predisposition to use specific drugs. During recent years considerable interest and excitement have been aroused by the discovery that the body produces its own opium-like substances, endorphins. The human brain has specific receptors for opiates, and these are concentrated in the pathways of the brain that are concerned with the perception of pain. It is speculated that opiate dependence in some people may be due to a genetically determined endogenous opioid deficiency.

It has been widely noted that most drug use is not attributable to any personality abnormalities. There is no unique "alcohol-dependent or heroin-dependent personality".

Drug-takers vary a great deal in their intelligence and there is little support for the view that drug use is caused in many cases by lack of intelligence. Evidence shows that drug takers are of average or above average intelligence.

Drug dependents in treatment institutions are often psychiatrically disturbed. It is possible that drug-taking satisfies disturbed psychological needs. It is possible that both psychiatric disturbance and drug taking may be caused by some other factor.

Most of the drugs that are used or misused have definite and usually relaxing effects. People who have high anxiety levels or other strong psychological needs find that drugs help them to adjust their unsatisfactory mental states to a more acceptable and bearable condition.

Many drug users certainly report that they do use drugs "to get high", "to feel relaxed", "for the experience". Often this motivation appears to be quite casual. Drugs can be fun, and often a reliable means of obtaining enjoyable experience. Many autobiographical accounts of drug use have described and emphasized the important appeal of these pleasant effects. Most drug use is indulged in as a facet of other leisure pursuits which are themselves widely considered a source of pleasure. Clearly, these people are not psychologically disturbed. They have only to be reminded that exhilaration and pleasure can be obtained by alternative methods like music, sports or mountaineering.

Why do people continue to take drugs inspite of the realisation of immense harm being done by them? The theory of self-destruction is offered; people have poor self-images and strong feelings of hostility directed at themselves.

Youthful illegal drug use is often a *symbolic gesture of defiance* against parental or authority values. Family disturbances, broken homes, loveless homes or excessive protection by parents, educational disturbance, social deprivation are all important environmental factors.

Youthful curiosity and peer pressure are the most important factors in the initiation and perpetuation of drug use. Most youthful drug-takers are introduced to drug use by friends of their own age and background, particularly those staying away from their parental homes in flats or hostels. Peer pressure generates strong social endorsement for using cannabis, LSD or even heroin, especially on impressionable youths. It is clear that people will normally only be influenced by those whom they regard as acceptable, if not exemplars; people whom they like and wish to be accepted by.

The emergence of a distinctive youthful drug culture during the 1950's and 1960's probably occurred for a variety of reasons. The use of cannabis received a certain amount of encouragement by North American musicians. Rock music, permissiveness and Hippie culture arrived in the 1960's with a heavy emphasis of rebellion against established conventional values and practices, and an increasing alienation or anomie. The music of the period was also explicitly drug-oriented ("psychedelic music") and further fostered the integration of drug use with the general youth culture. Instead of fitting into the rat-race of straight society with its long-term planning and deferment of gratification, the drug culture permitted instant enjoyment.

Education—the Way Out of the Tunnel

The scale of drug problem is enormous and apparently on the increase. It is very important therefore to consider what can be done to prevent such problems arising.

Health education should begin by parents themselves following healthy living practices which their children can imitate. A father who smokes or drinks alcohol is hardly the right person to teach his teenager son not to try "smoking grass".

The impact of health education is effectively nullified by commercial advertisements of alcohol, tobacco and tranquillizers. It has been suggested that there should be a total ban on advertising tobacco and alcohol. It is doubtful if such steps would produce any dramatic results.

Education is defined as an activity that modifies attitudes and behaviour. Attitudes to alcohol, tobacco and illicit drugs have taken decades, if not centuries to develop. It may take as long to change or improve these attitudes. We need a revival of the Ayurvedic emphasis on healthy living practices which ensure a *happy* life as well as a *good* life *(Swastha Vrutta* and *Sad Vrutta).*

4. PHYSICAL EXERCISE IN HEALTH AND DISEASE

Introduction

The importance of physi^al exercise for the maintenance of positive health has been appreciated since ancient times. The following passage from *Charaka Samhita* sums up the subject very well:

"That activity of the body, which is meant to increase its strength and firmness is regarded as physical exercise. It should be practised regularly in the right measure. Lightness, capacity for work, firmness, tolerance to hardship, subsidence of humoral discordance and stimulation of the gastric function accrue from exercise."

"Fatigue, exhaustion, wasting, thirst, asthma, cough, fever and vomiting result from over-exercise".

An important undesirable characteristic of modern life that distinguishes it from the past is the *low level of physical activity.* Epidemiological studies have suggested sedentary life style and associated overweight as important contributory factors in two very important diseases, diabetes mellitus and atherosclerotic arterial disease. The co-existence of the two diseases is common, and a major

cause of mortality and morbidity in diabetes mellitus is cardiovascular complications. The purpose of this chapter is to review the physiology of exercise and the evidence in favour of the role of exercise in the prevention and treatment of these two important diseases, and to raise the important question—are the two terms "physical exercise" and "Yogasanas" equivalent and interchangeable?

The Physiology of Exercise

The detailed study of muscular exercise began in the 18th Century when Antoine Laurent Lavoisier and Pierre Simon de Laplace discovered that the process consumes oxygen and produces carbon-dioxide. As investigation progressed it became clear that exercise involves not only the muscles but also many other tissues; indeed, it involves an extraordinary coordination of the respiratory, circulatory and nervous systems, all working together under highly integrated controls. During the 19th century almost every front-rank physiologist worked on muscular exercise at one time or the other. In the 20th century, A. V. Hill of Britain, August Krogh of Denmark and Otto Meyerhof of Germany have received Nobel Prizes largely for work relating to muscle or muscular exercise. In the years before World War II the Fatigue Laboratory at Harvard University became a world centre for the experimental study of muscular exercise.

A normal man at rest inhales between six and eight litres of air per minute, from which about 0.3 litre of oxygen is transferred in the lung alveoli to the blood. Simultaneously carbon dioxide is given off by the blood and exhaled. When the same man is engaged in maximal muscular activity he may take in 100 litres of air per minute and extract five litres of oxygen. The term "maximal oxygen intake" introduced by Hill in 1924 characterizes the upper limit of performance of an individual in a remarkably predictable way and has proved to be an extremely useful physiological tool. The maximal oxygen intake in the normal individual, however, has to do not with the capacity of the lungs for ventilation or diffusion but with the maximal pumping capcity of the heart. Maximal oxygen intake is therefore a fair index to circulatory capacity, given normal lung function.

In 1905 John Scott Haldane (father of the late J. B. S. Haldane) and John G. Priestley showed experimentally that lung ventilation can be doubled by increasing the amount of carbon dioxide in the inspired air from the usual negligible amounts to about 3 per cent. They postulated that the respiratory centre in the brain is primarily subject

to the influence of carbon dioxide in the arterial blood flowing into it. More refined studies later showed that Haldane's chemical control theory was an over-simplification. Whatever its exact modus operandi, the respiratory control mechanism ordinarily prevents carbon dioxide from accumulating in any significant degree and virtually assures an adequate supply of oxygen over a range extending from rest to maximal exercise.

Hill studied the effects of breathing pure oxygen during exercise. The immediate effect of switching during steady exercise from ordinary air to air enriched with oxygen is to lower considerably the rate of ventilation. Athletes who have breathed oxygen-enriched air during exercise have reported a pronounced relief of subjective distress and have evinced a decrease in ventilation. Oxygen breathing extended the work capacity of trained athletes. On the other hand the Mexico Olympics showed the adverse effect of high altitude and hypoxia (deficient oxygen) on competitive athletics.

Oxygen Debt

An important mechanism employed by the body when it is under fairly severe stress from exercise is its ability to incur an oxygen debt. Dr. Roger Bannister of England in 1954 (as a medical student) ran a mile in 4 minutes. Later, Peter Snell of New Zeland ran the mile in 3 minutes 54.4 seconds. Such amazing feats are possible because the body mechanisms enable the exercising body to live temporarily beyond its capacity for transporting oxygen to active muscles and to compensate for doing so during rest after the exercise. Ventilation and oxygen intake continue to remain higher than normal for some time after vigorous exercise stops. The term "steady state" is used by exercise physiologists to define a rate of work that can be performed for considerable periods of time without oxygen debt. During continuous activity such as walking steadily at three miles an hour for several hours, oxygen debt is built up rapidly at first and then levels off. Thereafter it may remain virtually unchanged for some hours. During violent activity it builds up rapidly and continuously until the activity ceases.

Normally arterial blood contains about 18 per cent oxygen by volume (carried by the haemoglobin of red blood cells), breathing pure oxygen raises this figure to 18.5 per cent. When a person is at rest, the tissues absorb oxygen at a rate that reduces the 18 per cent oxygen content of the arterial blood to about 12 per cent in the venous blood. The drop is known as the arterio-venous oxygen difference.

During exercise, on the other hand, the blood may have to give the tissues as much as 15 out of its 18 per cent of oxygen, about 2½ times more than at rest. The biological properties of haemoglobin play a very important role in enabling the body to adapt to exercise.

In a young man the heart can increase its output from about 5.5 litres of blood per minute at rest to nearly five times that figure during maximal exertion. At peak demand for oxygen the heart increases its output both by speeding up its rate of beating and by increasing the volume of blood pumped at each stroke. The pulse rate may double or triple, the stroke volume may go up from 60-80 millilitres per beat at rest, to as high as 120 millilitres per beat during exercise. Under moderate stress the heart may increase either its pulse rate or stroke volume, depending upon the individual's physical training and perhaps on other factors. The heart of a trained athlete increases its stroke volume more readily than that of a sedentary person. Under the stress of emotions such as fear and anger the heart increases its output almost entirely by speeding up its rate of beating. If the nerves controlling the pulse rate are blocked experimentally by drugs, however, the heart will expand its stroke volume. The increase in cardiac output during emotional stress is considerably less than it is under physical stress, not more than a third over the normal output at rest.

Redistribution of blood flow

The heart's capacity for increasing its output five-fold is not enough even allowing for the ability of haemoglobin to give up oxygen more freely, to account for the muscles' consumption of oxygen during violent exercise. An extra margin is provided by a change in the pattern of blood flow. During heavy exercise most of the arterial blood is diverted to the active muscles where the need for oxygen is most acute.

When the body is at rest, the muscles take up no more than about 20 per cent of the total body oxygen consumption; substantial amounts of oxygen go to the brain, the heart, the skin, the kidneys and other organs. If the muscles' share of the oxygen is about 20 per cent, they use at rest only 60 to 70 millilitres of oxygen (the body's total oxygen consumption at rest being 300 millilitres per minute). During exercise, as in running or swimming, the active muscles need about 3000 millilitres per minute, or about 50 times their resting requirements. The other body organs do not need anything like this increase of oxygen; in fact most of them actually use substantially less oxygen during maximal exertion. By adaptive mechanisms, all but a

relatively small portion of the increased cardiac output can go to the active muscles.

The muscle cell is extraordinarily tolerant to a temporary shortage in oxygen suppy, thanks to the presence in these cells of myoglobin. This substance, like haemoglobin carries oxygen but it surrenders its oxygen much less readily than haemoglobin, and serves as a special oxygen store for the muscle cell. An intermittently contracting muscle cell might recharge its myoglobin during the resting phase and then, during a succeeding contraction call on myoglobin oxygen stores. Short periods of work alternating with short periods of rest seem to be more efficient metabolically as well as in work accomplished than long work periods followed by long rest periods. The amount of myoglobin in muscle tissue can be increased by physical training.

Research on the physiology of exercise has important practical objectives, particularly with respect to what can be accomplished by physical training. The training methods of athletes, from the time of the Greeks to the present, have been largely empirical. With methods based rationally on fuller physiological knowledge there is room for improvement of human physical achievement, well within the bounds of safety.

Exercise and Diabetes Mellitus

An early as 600 BC Sushruta advised the affluent diabetic to indulge in vigorous physical exercise (such as walking twenty "yojanas", or digging a well). At the same time Sushruta exhorted the thin diabetic not to exert too much.

After the discovery of insulin, Joslin and Katsch in particular emphasized the importance of physical exercise as one of the three basic principles in the management of diabetic patients. The advent of oral hypoglycaemic drugs in the 1950's contributed to a slackening in the attitude of both physicians and patients towards the basic principles. Diet control, exercise and weight reduction needed sustained effort on the part of the patient, which in turn required strong motivation and constant vigilance. Swallowing a pill or two every day was so much more comfortable, and if it reduced the blood sugar, then why bother about physical exercise? Manufacturers of drugs would ensure drug promotion. Who would promote physical exercise and weight reduction?

The results of a ten-year prospective multicentric randomized clinical study by the University Group Diabetic Programme (UGDP)

comparing different treatment regimens gave a big jolt to everybody in the 1970's. The suggestion that a relationship existed between higher cardiovascular mortality and use of oral sulphonyl urea drugs was, to say the least, disquieting to both physicians and patients. The results have been subject of great controversy but the one good thing that has emerged from it is the *re-emphasis* on physical exercise and weight reduction as a primary modality of treatment in the maturity onset diabetes. A good physician today will give neither insulin nor oral drugs initially to asymptomatic diabetics in whom a diet and exercise regimen has not been first pursued sincerely. He will emphasize the need and method of regular physical exercise and weight reduction more aggressively than before.

What are the effects of exercise on diabetes? In 1887 it was discovered that the rate of glucose uptake is enhanced in the working muscles. Allen in 1919 demonstrated that exercise induces a fall in blood sugar and that it may improve acutely the tolerance to a carbohydrate load in the diabetic patient. On the other hand it was also appreciated that in poorly controlled ketotic diabetics, exercise may have deleterious effects. During the insulin era it was shown by Lawrence that exercise enhances the hypoglycaemic effects of subcutaneously injected insulin. When exercising and non-exercising children in juvenile diabetic summer camps were compared it was found that insulin requirements decrease on exercise. Goldstein et al described a muscular activity factor (MAF) released by exercising muscles which apparently stimulated glucose uptake even in non-contractile muscles. Subsequent studies however, could not confirm the MAF hypothesis.

Stimulation of glucose uptake during muscular exercise might depend upon increased binding of insulin to its receptors in muscle cells, resulting in *enhanced insulin sensitivity* even for the very small amount of insulin that may be present.

The increased fuel requirements of exercising muscles (free fatty acids, glucose) are met basically by increased production of three hormones, noradrenaline, adrenaline and glucagon, abetted by growth hormone and cortisol. Noradrenaline increases the rate of lipolysis and release of FFA from fat depot. Adrenaline increases muscle glycogenolysis upto six-fold during exercise and also mobilizes liver glycogen; it stimulates glucagon and inhibits insulin secretion. Glucagon plays a central role in the exercise-induced increase of hepatic glucose output.

Physical training results in improved myocardial performance, improved

oxygen transport as well as increased oxygen extraction by the muscles; the myoglobin levels are elevated; mitochondrial size and number increase, so also their enzyme content and activity. Hence for the same amount of oxygen extraction there is less metabolic and circulatory demand. There is decreased catecholamine activity in the trained subject. Exercise increases fibrinolytic activity of plasma, which is important since in diabetes, there is significant reduction in plasma fibrinolysis and a primary fibrinopathy may precede the metabolic and vascular abnormalities.

Currently there is wide-spread enthusiasm for *yogasanas* in diabetes. Compared to the exuberance of the enthusiasm for Yoga there is a remarkable paucity of hard data on the physiological effects of yogasanas, on the various circulatory and hormonal parameters, to compare with data derived from treadmill or supine bicycle exercise. The need for such studies cannot be too strongly emphasized. The type of exercise recommended by Sushruta (long walks, digging a well, wrestling, horse riding) is similar to the treadmill exercise which has been extensively studied. It may be erroneous to consider *that* type of exercise and Yogasans as interchangeable. In fact Yogasans may be acting in an entirely different manner.

The emphasis of Yoga is on mind control. One of the modern methods advocated for the control of blood sugar is by *bio-feedback mechanism*. In this technique muscular relaxation is obtained by the help of electromyograph. The idea behind this is that stress causes rise in blood sugar (through neuro-endocrine mechanisms), relaxation techniques would lower the same. Other data show that meditation helps to change the metabolic pattern from type A (overdrive of sympathetic nervous system) to type B (predominance of parasympathetic). Adrenergic drive is essential for competitive sports, and yogasanas for Indian olympic athletes might have actually reduced their performance (personal communication from Dr. Bhole of Kaivalyadham, Lonavala). The point to appreciate is that physical exercise and yogasanas are not interchangeable terms and the benefits derived from either of them may be mediated via entirely different mechanisms.

Exercise and Coronary Artery Disease

Atherosclerotic coronary artery disease has a multifactorial origin, of which each of physical activity and overweight (which are closely correlated) emerge as important contributory factors. Community settlements in Israel have an identical diet and life style for all inhabitants; those who have sedentary habits have shown two to four times higher

incidence of coronary heart disease as compared to more active people. The Framingham studies in USA have shown that physical activity increases HDL (high density lipoproteins) which have a *protective role* against development of atherosclerotic lesions. It has been found that HDL levels of less than 30 mg/dl are associated with twice as much risk of myocardial infarction as those with HDL over 60 mg/dl,. Vigorous exercise like jogging raises HDL to the desirable range. Several reports have indicated that increased physical activity, both at work and at leisure, is associated with diminished risk of myocardial infarction (heart attack). More and more people are therefore now engaging in such physical activities as jogging, golfing, swimming etc. as part of their health programme.

Not many years back, patients of myocardial infarction were advised prolonged rest and a somewhat resigned life. Today the pendulum has swung to the opposite side. Early ambulation and high levels of physical activity are now widely recommended in many patients who have recovered from myocardial infarction. Participation of such patients in marathon races (which perhaps represent the ultimate in physical exertion and endurance) is a testimony to what aggressive rehabilitation under supervision can be achieved. On the other hand non-supervised indulgence in jogging by enthusiasts has led to some sudden deaths. Hence it is worth examining critically the exact contribution of exercise in coronary patients.

Eckstein in 1957 produced ischaemia in dogs experimentally by ligating their coronary arteries. In one set of dogs, after 48 hours the animals were put on a treadmill; many developed ventricular aneurysms; another set of dogs was rested for seven days after ligation and then put on a treadmill for exercise; they demonstrated development of collateral circulation. This attractive idea that exercise induces development of collaterals has strongly motivated physicians and patients to take up enthusiastically to physical exercise. It must be stated however, that similar experiments in rats failed to confirm this. Gregg in 1974 observed that there is really no experimental evidence that physical exertion improves the collateral circulation in the normal heart.

However, evidence that human coronary artery disease can *regress* has been provided in studies on swine and primates and in serial human coronary angiographies. Exercise by inducing higher levels of HDL probably contributes to this regression. Control of high blood pressure and complete stoppage of cigarette smoking are the other two contributory

factors aiding the regression or non-progression of lesions. But it is worth noting that the *type* of exercise that is considered essential is *dynamic* muscular exercise of sufficient *magnitude and duration:* it should raise the pulse rate to at least 70 per cent of the maximum attainable for the age and sex (say over 120 per minute for a man of 55), which should be sustained for at least 30 minutes, at least 3 days in a week preferably on non-successive days. Fast walking, jogging, bicycling, swimming are the examples of dynamic muscular exercise.

During the last ten years I have done executive health check-up of over 5000 middle aged healthy individuals and a routine question regarding physical exercise elicits from many persons a reply: "I do Yoga for 10 minutes every day". Here again physicians as well as patients seem to use the two terms as if they are interchangeable. The haemodynamic and metabolic changes associated with 45 minutes of vigorous dynamic muscular exercise will probably be entirely different from the "ten minute yoga". I am looking for hard data on metabolic, hormonal and haemodynamic effects of Yogasanas, to match the claims made and enthusiasm shown by their adherents. The sophisticated methods are now available to us to substantiate and validate the beneficial effects if any.

On the other hand yoga might be producing its benefits by an entirely different mechanism from that discussed under dynamic muscular exercise. The conversion of Type A coronary prone personality to Type B has been discussed earlier. Increased adrenergic activity is an important contributory factor, especially in the onset of dangerous arrhythmias. Reduction of adrenergic activity by means of beta-blockers or by yoga and meditation would be beneficial. The motivation and attitude towards health-related behaviour (refraining from smoking, control of caloric intake, a more relaxed attitude by practising "Shavasan") of the health conscious individual may be important contributory factors, irrespective of the direct contribution of exercise and yogasanas.

The scientific method demands validation of any proposition. Uncritical acceptance and uncritical rejection are both equally inimical to the spirit of science. Open-minded curiosity about any claims of benefit by any mode of therapy or procedure, and healthy scepticism about claims till validation is established, make an ideal blend in a scientific mind. This way one would safeguard against missed opportunities and false hopes about Yogasanas.

I end up by making a plea for an increasing network of play grounds, gymnasiums and sporting facilities of *all* sorts, and promoting their full utilization as a means of promotion of positive health.

Chapter 15

EXPLORING THE HERBARIUM

Introduction

According to Charaka, "There never was a time when the science of life did not exist, even as it was the case with life". The life-stream carried in its currents its own supporting and protecting wisdom that became manifest at the beginning of each cycle of time to the seers. Man guided by the instinct of lower animals and the intuition of his own species evolved the science of drugs from the vegetables and animal and mineral sources around him. In *Atharva Veda,* the precursor of Ayurveda, one finds the following interesting description:

"The boar knows the plant; the mongoose knows the remedial herb; what ones the serpents, the Gandharvas know, those I call to aid. What herbs of the Angirasas the eagles know, what heavenly ones the Raghatas know, what ones the birds and the swans know, and what all the winged ones, what herbs the wild beasts know, these I call to aid for you. Of how many herbs the inviolable Kine partakes, of how many the goats and sheep, let so many herbs, being brought, extend protection to thee".

— *Atharva Veda, Kand 8, Sutra 7.*

Charaka states, "The goatherds, the shepherds and cowherds and other foresters are acquainted with the names and forms of plants; and their uses".

Learning from Instinct of Animals

One striking example of the instinct of animals in relation to plants, is provided by the milkweed *Asclepias curassavica* in Costa Rica. Although it grows abundantly in the grass, large herds of cattle completely avoid it, because they have learnt by experience that it causes sickness and occasional death. The poisons in the asclepiads have attracted much attention among the pharmacologists and organic chemists because the

substances are similar to digitalis, the cardiac glycoside. The amount of the glycoside that causes vomiting is just about half the amount required to cause death through its action on the heart. Hence an animal that eats a grass containing the cardiac glycoside will, provided that it is capable of vomiting, rid itself of the poison before a lethal amount can be ingested.

In contrast, milkweeds are the exclusive food of the larvae of an entire group of tropical insects which include the monarch and the queen butterflies. Insect-eating birds avoid these butterflies Assay of extracts of the butterflies have revealed cardiac glycosides similar to digitalis in their effect — calactin, calotrophyin and calotoxin. The fact that many naturally occurring plant poisons including alkaloids and cardiac glycosides are bitter is highly relevant. The bitterness is a clue for conditioning predators to avoid the plants. The poison itself could very well be tasteless, provided that it was always associated with a flavour that could shy away the predators. Certain plants exhibit a form of mimicry — they have flavours usually associated with particular poisons but actually lack the poison — still the ploy works to shy away the predators! Analysis of plant selection by the butterfly group (whose caterpillar stage is a formidable eating machine) has made it clear that their choice has a chemical basis.

The plant world's main line of defence (against attack by insects and birds and animals) consists in chemical weapons. Very wide-spread among the plants are certain chemicals that apparently perform no physiological function for the plants themselves but do act as potent insecticides, or insect repellents. Among those are alkaloids, quinones, essential oils, glycosides, flavonoids and raphides (crystals of calcium oxalate). Long before man learned to synthesize insecticides he found that an extract from chrysanthemums, *pyrethrin,* which is harmless to mammals, is a powerful killer of insects.

Particularly interesting are the *alkaloids,* a heterogeneous group of nitrogenous compounds found mainly in flowering plants. They include nicotine, caffeine, quinine, marijuana, opium and peyote (mescaline). Alkaloids give the plants that contain them protection from predators. Plant alkaloids can disturb an herbivorous animal's physiology, and hallucinogenic alkaloids may be "chemopsychological weapons". It is even possible that plants fight insects with tumour-inducing substances; at least one plant alkaloid, nicotine, is known to be a powerful carcinogen in vertebrates.

Through accident, through trial and error and through intelligent observation & inference, mankind has accumulated knowledge about harmful plants (poisons) and useful plants (drugs). As early as 5000 B.C., the Chinese had well developed floral pharmacopoeias, or sets of accepted plant-derived drugs. So did the Babylonians, the Assyrians and the Hebrews. The Greeks knew many of the currently used plant-derivative drugs. Dioscorides produced in 60 A.D. the great De Materia Medica, which dealt with all the medicinal substances known at the time, including some 600 plants. The *Charaka Samhita* describes 500 herbal drugs and the *Sushruta Samhita* describes 700 plants classified under 37 classes or *"ganas"*.

There are as many as 800,000 species of plants on earth of which only a few have been exploited by man. The three major cereals —rice, wheat and maize — and perhaps ten other widely cultivated plant species stand between famine and survival for the majority of the world's human population. A handful of drug plants have served mankind for several thousand years. Table I gives a list of important drugs (and poisons) that originated in folklore and form part of the pharmacopoeia even today. To the ancient Greeks, the word "pharmakon" meant not only a curative drug but also a poison, a charm, a spell, or an incantation. Today the word drug still has all these meanings.

Today we understand the nature of drug action a lot better than at any time in history, and our interest in the herbarium continues even today. A most recent example of a herbal remedy of great interest in the 20th century is Qinghaosu, a medicinal herb used in China since 168 B.C. Chinese chemists have in 1972 isolated the active principle and used it successfully in Chloroquin-resistant Plasmodium falciparum malaria.

Chemistry of Plant Products

As knowledge of chemistry advanced, many plants were subjected to chemical analysis to obtain active principles in pure forms. Thus Serturner and Pelletier in Germany isolated active principles from opium and pomegranate peal. With rapid advances in organic chemistry after Wohler's synthesis of urea, there was a great spurt of activity in the field of synthetic chemistry. Today a large majority of drugs in therapeutic use are synthesised. However, pharmacopoeias of most countries still contain a fair number of drugs obtained from the vegetable kingdom.

TABLE I

Name of Drug	*Family or Genus*	*Part of Plant*
Atropine	Atropa Belladona (Solanaceous family)	Whole plant
Castor Oil	Castor Oil Plant	Seeds
Caffeine	Coffea arabica Thea sinensis	Seeds
Cannabis Indica	Indian Hemp	All parts
Clove	Caryophyllata	Flower
Cocaine	Erythroxylon Coca	Leaves
Colchicin	Colchicum autumnale	Roots and Seeds
Digitalis	Fox glove (Purburea)	Leaves
Emetine	Ipecacuanha	Roots
Ephedrine	Ephedra	Stems
Eserine	Calabar beans (physiostigma venenosum)	Seeds
Forskolin	Coleus Forskohi (Mainmul)	Fresh roots
Morphine	Papaverum somniferum	Unripe capsule
Nicotine	Nicotina (tobacco)	Leaves
Picrotoxin	Anamitra Cocculus	Mushroom
Pyrethrum	Pyrethri flores	Flower
Quinine	Cinchona (Quina quina)	Bark
Quinghaosu		
Reserpine	Sarpagandha (Rauwulfia serpentina)	Roots
Salicylic acid	Willow	Bark
Scillaren	Squill	Bulbs
Senna	Cassia acutifolia	Leaves
Strophanthus	Strophanthus gratus	Seeds
Strychnine	Nux Vomica	Seeds
Tubocurarine	Curare (C. tomentosum)	Bark & Stems
Turpentine	Pine (coniferous tree)	Resin from bark
Vencristine	Vinca Rosae	Flowers

Various parts of a plant may be used as therapeutic agents. These may be used in a dried form or after extractions. Such crude preparations of plant origin are called Galenicals after Galen, the ancient Greek physician.

Chemical analysis of active principles derived from plants shows they are glycosides, saponins, alkaloids, oils, waxes, resins, compound resins, carbohydrates (gums), tannins.

The pharmaceutical preparations of plant origin are administered either as *watery* solutions (including mucilages, syrups and elixirs containing syrups & alcohol), or *alcoholic* solutions, or *extractives — infusions, decoctions, tinctures fluid extracts, solid extracts etc.*

Alkaloids

The alkaloids are a class of compounds synthesized by plants. Many of them have powerful effects on the physiology of animals and man. Since earliest times they have served man as medicines, poisons and the stuff that dreams are made of.

The alkaloid *morphine,* the principal extract of the opium poppy, remains even today, "The one indispensable drug". *Quinine,* from Cinchona bark, cures malaria even today. *Colchicine,* from the seeds and roots of the meadow saffron, banishes the pangs of gout. *Reserpine,* from snake roots or Sarpagandha, tranquillises the anxieties of the neurotics and psychotics. The coca leaf alkaloid *cocaine* plays Jekyll and Hyde as a useful drug and as a sinister narcotic. The South American arrow poison *tubocurarine* is used today as a muscle relaxant during surgical operations. The belladona alkaloid *atropine* is a useful antispasmodic and mydriatic (dilates the pupils). The alkaloid derived from Calabar beans, used by West African tribes in trials by ordeal, *physostigmine* is specific treatment for myasthenia gravis. *Caffeine* and *nicotine,* the most familiar of the alkaloids are imbibed and inhaled daily by a large segment of the human population. *Coniine,* the alkaloid poison in the draught of hemlock that killed Socrates, has a simple structure while *Strychnine* from nux vomica has a complicated structure. From the chemical point of view they are all grouped together only because we do not know enough about them to file them under other headings. One common thing is that amino-acids are the source of most alkaloids. From the same starting material tyrosine, one plant makes reserpine while the other makes strychnine. *Hordenine* is one of the few alkaloids known to undergo further metabolism in plants; it is

converted into one of the units that form the long chain molecules of lignin, an essential structural material in many plants.

Lectins

Lectins are proteins found primarily in plants. They combine specifically with sugars on cell surfaces and hence bind cells together. The legumes are particularly rich in lectins. In recent years, lectins have provided a valuable tool for research in immunology, since lectins are valuable as probes for identifying and mapping the sugars on the surface of cells.

It has been known for many years that protein extracts of various bean species are able to induce lymphocytes to proliferate. The term *mitogen* is used for these substances because of their ability to stimulate mitosis. The most widely used substance in the immunological sphere is *phytohaemagglutinin* (PHA) and its mitogenic activity was noticed during its use as an haemagglutinating agent in haematology. This mitogenic effect is antigenically non-specific, but most of the mitogens (PHA, Concavalin A, leuco-agglutinin) have been shown to stimulate T lymphocytes. Pokeweed mitogen is believed to be primarily a B lymphocyte stimulant and specifically so in low concentrations. While the actual nature and significance of non-specific stimulation of lymphocytes is not understood in general, there is a fair degree of correlation between cellular immune competence and non-specific T-cell stimulation by mitogens. In the study of human disease states, a very large majority of the work has used PHA as the mitogen.

In the 1890's, with the help of ricin & abrin, Paul Ehrlich discovered some of the most fundamental principles of immunology.

Hormones from Plants

After the establishment of the structure of cholesterol in 1932, interest was focused on *plant steroids* as a fertile route for the production of steroid hormones. Digitalis, the cardiac glycoside extracted from plants which had been known for centuries as poisons, was shown to contain a steroid attached to a sugar. The steroid part has a skeleton like that of a bile acid, but one major difference is that the side chain is coiled into a ring.

The digitalis steroids are rather special, but steroids with sugars attached are very common in the plant world. One class of these substances is known as *Saponins,* because watery solutions of these

foam like soap when shaken. The steroid part of a saponin is called a sapogenin. The most interesting of these substances is *diosgenin,* which has a skeleton remarkably like that of cholesterol, with 27 carbon atoms and a double bond between the 5th and 6th carbons. The discovery of this structure at once suggested that diosgenin would be useful for producing sex hormones. Diosgenin could easily be converted into pregnenolone, already known as a building material for progesterone.

Another substance called *sarmentogenin* which had been isolated in 1929 from some unknown plant seeds, was shown to carry a hydroxyl group at the position 11, suggested the possibility of converting it into cortisone.

Ethnobotanical Research

Folklore has been considered as the archaeology of the mind. The knowledge about plants that has been accumulated through experience, trial & error, and which has been passed on from generation to generation, whether verbally or in writing, forms the main subject of ethnobotany. The science of ethnobotany has recently received much attention in underdeveloped and developing countries, where large portions of populations still depend upon natural resources in practically indigenous conditions and the impact of modern systems of medicine has not reached them.

Ethnobotanical information is largely based on personal experience of groups of people or tribes, where human beings themselves served as tools of experiments under force of circumstances. It might have cost many human lives over the millennia, to eliminate certain harmful drugs from folk medicine, but there might have been some real gains.

A considerable percentage of India's population comprises tribals. Certain parts of India have predominantly tribal populations such as Central India, the eastern parts of peninsular India and most of the far-eastern states. Ethnobotanical researches have so far brought on record over 500 plants as significantly used by the tribals for various purposes. Organized field work in this subject was started by Dr. S. K. Jain, Director, Botanical Survey of India, in 1960 and an active school of ethnobotany has now come up in this department. The first group of people taken up for studies were the Gonds in Central India, and the work was extended to Bihar, Orissa, Andhra Pradesh, Arunachal Pradesh, Meghalaya and Manipur. A list of 50 plants used in folk medicine in different parts of India is given by Jain. The uses extend

over eye diseases, diarrhoea and dysentery, cough and cold, fever, wounds & fractures, dog bites, snake bites, abortifacients and aphrodisiacs. Of particular interest is the *saprosma ternatum,* a decoction of its leaves being used with ginger in malaria. This deserves further scrutiny in view of the search for new anti-malarials. Similarly *Tamarix ericoides Rotty* (Tamaricaceae) leaves as a decoction are reported " to cure enlarged spleen in children as well as in adults", and it is worth scrutinising it for anti-malarial effects.

Ethnobotanical studies should be profitably utilised for interaction between organized traditional medicine and folk medicine. Most of the primitive tribals will not accept any other medicine except the ones prescribed by their medicine-men. The medium of the medicine-men should be profitably utilized for a choice of appropriate medicines for further critical scrutiny. The immense richness of botanical resources was emphasized by Schultes in 1963 when he pointed out that only a very small fraction of plant resources has yet been utilized by the human race, particularly for their active principles. A study by Schultes in 1969 on hallucinogens of plant origin has yielded results of academic and practical interest. Ethnobotanical research leads to the discovery of new or less-known medical herbs and gives new clues for pharmacological testing. Herbarium sheets and museum specimens and field notes on them have provided a good source of ethnobotanical data.

Jain has discussed the problems related to the authenticity of information collected during ethnobotanical field work. Many plants are referred in literature to their common names and their identity may be disputed. About 20 different plants are attributed to the name SOMA mentioned in the ancient Hindu epics. Other significant examples of disputed identity are the names "Brahmi", "Punarnava", "Jatamanasi", "Rudanti", "Bala" and "Kalpavruksha". The main difficulty in fixing the botanical identity of herbal drugs is the lack of proper descriptions and illustrations. Local names for plants or plant products have not remained the same over the ages. The properties attributed to plants are of help in identification in some cases, brief notes on the structure or morphology of plants but they may lead to greatly varying interpretations. For instance, the description of "SOMA" could be interpreted to tally with branded shrubs like *Sarcostemma* and *Ephedra* on the one hand, climbers like *Cocculus hirsutus* or *Dioscorea bulbifera,* and a polyporus fungus *Ammanita muscaria.* The botanical names of course mean little to the folks in the forests, rural or tribal

areas, or, for that matter to the non-botanists. Even the names common in commerce may be completely unknown and foreign to the tribal societies. Thus, if their help is solicited for procuring materials for testing, they will have to be told the names which are familiar to them, and to know these the only means is to do ethnobotanical work with them.

Screening of the plant kingdom for new substances of pharmacological value is a continuous quest.

Screening of Indian Plants for Biological Activity

The Central Drug Research Institute (CDRI) at Lucknow started in 1964 a programme for the screening of plant extracts for a wide range of biological activities. The botanical identity of each plant was established before the extract was prepared. Although it is customary to prepare extracts of plant material with a variety of solvents (polar & non-polar) when investigating possible biological effects, they used only a 50 per cent ethanol extract in order to be able to cover a large number of plant material. Almost all these extracts have been tested for antibacterial, antifungal, antiviral, anticancer and a wide range of pharmacological activities. A fair number of extracts have been tested for anti-amoebic, antimalaria, antifilaria and hypoglycaemic activity and a few for activity against helminths and spirochetes and for inhibition of spermatogenesis and prevention of fetal implantation. Antilipemic, diuretic and anti-inflammatory activities were also tested. In all, *2065* extracts from 1973 species were studied. However, in terms of clinical applicability, the bulk of this colossal effort has turned out to be sterile.

Phytoconstituents are known to vary depending on ecological factors such as time of collection, habitat, climate etc. This may explain the discrepancy sometimes found between observations of different workers. Hence time and place of collection should be mentioned along with the experimental data.

Indian folklore and Ayurvedic pharmacopoeia mention the use of some plant products as local contraceptives. The CDRI, Lucknow has tested about 1600 plant extracts (50% ethanol) for in vitro spermicidal activity on rat vasal or epididymal contents at 2% concentration. Thirty plant extracts showed spermicidal activity in rats and sixteen out of them caused instantaneous immobilization of human spermatozoa.

The list of extracts which have shown promising activity at the CDRI is given in *Appendix I.*

Anti-tumour Plant Agents

Comprehensive reviews of the technical and folklore literature have been published by Hartwell in 1971, wherein citations are recorded for the use of different plant species which have been used or recommended in various parts of the world for the treatment of cancers and other conditions such as warts and tumours. In the U.S.A., the Cancer Chemotherapy National Service Centre (CCNSC), now incorporated into the Development Therapeutic Programme (DTP) has screened thousands of plant extracts against standard tumour sytems consisting of solid tumours and leukemias.

At the Cancer Research Institute (CRI) in Bombay, more than 600 species of indigenous plants have been screened using standard transplantable tumours. Eight plants have exhibited meaningful anti-cancer properties. Phytochemical studies, subsequently undertaken on plant materials, have revealed that some of them contain chemical entities which manifest various degrees of activity in experimental tumours. Isolation and structural elucidation of plant-derived tumour inhibitors are yielding fascinating, novel types of growth-inhibiting compounds containing high electrophilic functions. New compounds possess structures and chemical properties which suggest that they may act by selective alkylation of growth-regulatory macromolecules. This approach may yield useful templates for the synthesis of potentially superior chemotherapeutic agents. New growth inhibitors may provide powerful tools for the elucidation of new biochemical mechanisms of growth control that may be amenable to selective regulation.

Dr. Ramakrishna Ambage of CRI has reviewed information on some promising plants, novel isolates, their anti-tumour properties and possible mechanisms of action. The most interesting ones appear to be the diterpenes, lignans, quassinoids, ansamacrolides and alkaloids. The X, B unsaturate lactone function has been shown to be important for the tumour inhibitory activity of several classes of cyclic synthetic compounds and naturally occurring terpenoids.

It is evident that anti-cancer activity is encountered in compounds of a wide variety of chemical classes. Many of these are of novel chemical structures, especially those of considerable complexity, requiring the development of methods for the creation of new ring systems.

APPENDIX I
ANTI-CANCER

Serial No.	CDRI Code No.	Plant	Activity confirmed	Activity low
1	41	RT Berberis asiatica	+	
2	36	ST Cedrus deodara	+	
3	113	RT Calotropis gigantea	+	
4	18	LF Erythrina suberosa	+	
5	6	BU Urginea indica	+	
6	583	PX Annona squamosa	+	
7	380	PL Bacopa monnieri	+	
8	598	PX Buchanania lanzan	+	
9	428	RT) LF) Calotropis procer^	+	
10	443	PL Celsia coroma..deliana	+	
11	477	PL Cleistanthus collinus	+	
12	433	PX Cocculus pendulus	+	
13	554	PL Corchorus aestuans	+	
14	542	PX Cotoneaster marginatus	+	
15	390	PX Flemingia chappar	+	
16	513	PL Gleichenia linearis	+	
17	483	PL Ipomoea leari	+	
18	454	PL Lepidagathis trinervis	+	
19	328	PX Lyonia ovalifolia	+	
20	459	PX Maba buxifolia	+	
21	590	PX Manilkara hexandra	+	
22	303	SB Melia azedarach	+	
23	557	PL Nicotiana plumbaginifolia	+	
24	326	PL Polygonum recumbens	+	
25	306	SB Quercus semicarpifolia	+	
26	511	PL Selaginella plumosa	+	
27	478	PX Streblus asper	+	
28	469	ST) FR) Zizyphus rugosa	+	
29	723	Albizzia procera	+	
30	677	Casearia verca	+	
31	673	Duabanga sonneratioides	+	
32	613	Luffa graveolens	+	
33	654	Photinia integrifolia	+	
34	724	'Pyrus pashia	+	
35	732	Rhus parviflora	+	

Serial No.	*CDRI Code No.*	*Plant*	*Activity confirmed*	*Activity low*
36	637	Tetrastigma serrulatum	+	
37	952	PX Aglaia odoratissima	+	
38	938	PX Mallotus stenanthus	+	
39	958	PX Mappia foetida	+	
40	1474	PX Anamirta cocculus	+	
41	1377	PX Anisomeles malabarica	+	
42	1266	SB Castanopsis indica	+	
43	1441	PL Commelina undulata	+	
44	1442	PL Cyanotis fasciculata	+	
45	1446	PX Gymnosporia wallichiana	+	
46	1214	PL Jussiaea suffruticosa	+	
47	1448	PX Passiflora foetida	+	
48	1281	PX Tephrosia candida	+	
49	1212	SB Terminalia paniculata	+	
50	1365	PX Wikstroemia indica	+	
51	1528	PX Argyreia involucrata	+	
52	1523	PX Brucea mollis	+	
53	1522	PX Hippocratea macarantha	+	
54	1586	PX Indigofera mysorensis	+	
55	1603	PL Senecio tenuifolius	+	
56	1601	PL Vanda parviflora	+	
57	1584	PL Vicoa indica	+	
58	2068	PX Aglaia roxburghiana var. beddomei	+	
59	2090	PL Amberboa ramosa	+	
60	1872	FL Blepharis sindica	+	
61	1871	PL Cistanche tubulosa	+	
62	1865	RT Crotolaria burhia	+	
63	2050	PL Eranthemum purpureaum	+	
64	2100	PX Gmelina asiatica	+	
65	2081	PL Impatiens balsamina	+	
66	1961	PL Inula cappa	+	
67	2099	PX Ipomoea dichroa	+	
68	2055	PX Moringa oleifera (Hybrid)	+	
69	1936	PL Parthenium hysterophorous	+	
70	2097	LF Sansevieria cylindrica	+	

List of Plants Fractionated for their Biological Activity

HYPOGLYCAEMIC

Serial No.	*CDRI Code No.*	*Plant*	*Activity confirmed*	*Activity low*
1	54	RT Aegle marmelos	+	
2	89	LF Anacardium occidentale	+	
3	70	SB Ficus racemosa	+	
4	47	FR Mucuna prurita	+	
5	126	SB Quercus lancaefolia	+	
6	58	RT Ricinus communis	+	

C. N. S. DEPRESSANT

1	1244	PX Atylosia trinervia var. major	+	
2	1404	PL Geranium ocellatum	+	
3	1249	PX Melianthus major	+	
4	1592	PX Ardisia neriifolia	+	
5	1596	PL Cissus repens	+	
6	1594	PX Dysoxylum binectariferum	+	
7	1597	PL Forrestia mollissima	+	
8	1723	PX Saraca indica	+	
9	1621	PX Terminalia arjuna	+	
10	1847	PX Acacia auriculiformis	+	
11	1850	RT Boerhaavia chinensis	+	
12	1894	PL Cassia pumila	+	

HYPOTENSIVE

1	78	SB Alstonia scholaris		
2	262	LF Rhododendron arboreum	+	
3	379	SD Argyreia speciosa	+	
4	433	PX Cocculus pendulus	+	
5	387	PL Croton bonplandianum	+	
6	409	PX Hibiscus rosa-sinensis	+	
7	301	LF Kydia calycina	+	
8	584	SB Madhuca indica	+	
9	838	Ammania sengalensis	+	
10	623	Bridelia stipularis	+	
11	688	Chukrasia tabularis	+	
12	863	Cochlospermum religiosum	+	
13	602	Desmodium pulchellum	+	

Serial No.	*CDRI Code No.*	*Plant*	*Activity confirmed*	*Activity low*
14	876	Eriolaena hookeriana	+	
15	787	Kalanchoe integra	+	
16	814	Rhododendron nilagirica	+	
17	859	Zizyphus oenoplia	+	
18	1278 RT	Coleus forskohlii	+	
19	1487 SB	Miliosma pungens	+	
20	1339 PX	Rhododendron falconeri	+	
21	1925 PX	Aspidopterys indica	+	
		SPASMOLYTIC		
1	150 PL	Adiantum caudatum		+
2	247 LF	Actinodaphne angustifolia	+	
3	7 SB	Myrica nagi		+
4	274 PL	Pyracantha crenulata	+	
5	379 SD	Argyreia speciosa	+	
6	487 PL	Pholidota articulata	+	
7	973 SB	Balanites aegyptiaca	+	
8	1371 PX	Ancistrocladus heyneanus	+	
9	1278 RT	Coleus forskohlii	+	
10	1642 PX	Clausena pentaphylla	+	
11	1647 PL	Hydrocotyle podontha	+	
12	1947 PX	Acacia sundra	+	
		SPASMOGEN		
1	32 ST	Symplocos crataegoides	+	
		CARDIOTONIC		
1	57 PL	Asclepias curassavica	+	
2	1049 PX	Strophanthus wallichii	+	
		ANTI-INFLAMMATORY		
1	684	Saggittaria sagittifolia	+	
2	1192 PL	Hedychium spicatum	+	
3	1759 PX	Cyathea gigantea	+	

Serial No.	*CDRI Code No.*	*Plant*	*Activity confirmed*	*Activity low*
4	1758 PX	Cytherexylum subserratum	+	
5	1594 PX	Dysoxylum binectariferum	+	
6	1739 PX	Jambosa lacta	+	
7	1794 PL	Sonchus brachyotus	+	
8	2011 PL	Astragalus chlorostachys	+	
9	2044 PL	Desmodium laxiflorum	+	
10	2038 PL	Dioscorea pentaphylla	+	
		ANTI-STRYCHNINE		
1	85 LF	Leea indica	+	
		ANTI-ACETYLCHOLINE		
1	168 PL	Siegesbeckia orientalis	+	
		DIURETIC		
1	505 PL	Dryopteris crinipes	+	
2	524 PL	Pavetta indica	+	
3	521 PL	Vittadinia australis	+	
4	1747 PX	Linociera malabarica	+	
5	1763 PX	Pithecolobium bigeminium	+	
6	1725 PL	Plantago lanceolata	+	
7	1501 PL	Psychotria monticola	+	
8	1723 PX	Saraca indica	+	
9	2030 PX	Ficus elastica	+	

From the academic point of view, one would be interested in the mode of action of these diuretics in the light of current knowledge of diuretic action.

From the practical point of view, one will have to consider what will be the particular advantages of these herbal diuretics in competition with the currently available diuretics like the benzthiazide etc.

ABORTIFACIENT

1	1768 PL	Acrostichum aureum	+	
2	1581 PL	Perilla frutescens	+	
3	1766 PL	Verbena bonariensis	+	

ANTIBACTERIAL

Serial No.	CDRI Code No.		Plant	Activity confirmed	Activity low
1	579	RT	Arnebia nobilis	+	
2	779		Picea abies	+	
3	1238	PX	Evodia lunu ankenda	+	
4	1663	PX	Derris scandens	+	
			ANTIHISTAMINIC		
1	32	ST	Symplocos crataegoides	+	
2	1764	PL	Smithia conferta	+	
			SPERMICIDAL		
1	1639	PL	Aeschynomene indica	+	
2	1592	PX	Ardisia neriifolia	+	
3	1573	PL	Caltha palustris	+	
4	1679	PX	Clerodendrum serratum	+	
5	1662	PX	Samanea samar	+	
6	1684	PX	Schefflera capitata	+	
7	1685	PX	Symplocos gardneriana	+	
8	1703	SD	Trigonela foenumgraecum	+	
			ANTI-AMPHETAMINE		
1	197	PL	Fagonia cretica	+	
2	398	RH	Alpinia galaega	+	
3	329	PL	Conyza stricta	+	
4	351	LF	Dillenia indica	+	
5	354	PX	Mikania cordata	+	
6	749		Aesculus punduana	+	
7	689		Hiptage benghalensis	+	
8	1075	RH	Colocasia fornicata	+	
9	933	PX	Daphne papyracea	+	
10	1069	RH	Ipomea paniculata	+	
			ANTI-VIRAL		
1	50	Pod	Cassia fistula	+	
2	51	SB	Cassia fistula	+	
3	208	PX	Cassia auriculata	+	
4	621		Bridelia retusa	+	

ANTI-FUNGAL

Serial No.	*CDRI Code No.*	*Plant*	*Activity confirmed*	*Activity low*
1	579	RT Arnelia nobilis	+	
2	1204	PX Hypericum mysorense	+	
		NEUROMUSCULAR BLOCKADE		
1	340	RT Cocculus laurifolius	+	
		SEMEN COAGULANT		
1	1620	SB Albizzia odoratissima	+	
2	1629	FR Caesalpinia coriarua	+	
3	1582	PX Callitris robusta	+	
4	1707	PX Cassia javanica	+	
5	1600	PX Cupressus funebris	+	
6	1748	PX Diospyros insignis	+	
7	1777	PX Embelia viridiflora	+	
8	1548	PX Eriolaena quinquelocularis	+	
9	1599	PX Eucalyptus cloeziana	+	
10	1612	PX Garcinia indica	+	
11	1651	SB Grewia tiliaefolia	+	
12	1737	PX Humboldtia brunonis	+	
13	1718	PX Ixora coccinea	+	
14	1518	PX Leea acquata	+	
15	1740	PX Syzygium montanum	+	
16	1795	PX Tectaria cicutaria	+	
17	1621	PX Terminalia arjuna	+	
18	1502	PX Vaccinium pleschnaultti	+	
19	1749	PX Vateria indica	+	
20	1771	PX Vatica chinensis	+	
21	1589	PX Wendlandia wallichii	+	
		HYPERTENSIVE		
1	1871	PL Cistanche tubulosa	+	
2	1245	PX Sophora glauca	+	
		ANTIFERTILITY		
1	1822	PL Lamium album	+	
2	2055	PX Moringa oleifera (Hybrid)	+	
		ANTI-HELMINTHIC		
1	2036	TU Homordica dioica	+	

Chapter 16

PHARMACOLOGY, ANCIENT AND MODERN

Introduction

Ancient Indian Medicine had attained a very high degree of sophistication in its consideration of drugs and their classification according to their conceived modes of action. Considering that the main intellectual tool at their disposal was empiric observation, one marvels at the great width and depth of their conceptual thinking about drugs. In addition, one finds appreciation of certain basic principles in therapeutics which are valid even today. Examples:

"Medicine is of two kinds — one kind is promotive of vigour in the healthy; the other, destructive of disease in the ailing".

"The opposite of medicine is also of two kinds — one causing immediate disorders and the other causing remote ill effects".

"He is the best physician who knows the science of the administration of drugs with due reference to the clime and season, and who applies it only after examining each and every patient individually".

"A drug while inducing therapeutic effect should not evoke untoward effects".

"A drug that is not understood perfectly is comparable to poison, weapon, fire and the thunderbolt; while the perfectly understood drug is comparable to ambrosia".

"The drug whose name, form and properties are not known, or the drug which though known, is not properly administered, will cause disaster".

"The art of prescription depends upon the knowledge of dosage and time and on this art depends success. Hence the skilful physician stands even superior to those possessing merely a theoretical knowledge of drugs".

"The physician, endowed with a good memory, well-versed in diagnosis and the application of therapeutic agents, self-controlled and prompt in taking right decisions, is entitled to undertake treatment by prescribing these drugs".

Ayurvedic Materia Medica

Drugs are derived from vegetable, animal and mineral origin. Sushruta has classified drugs according to their properties into 37 *"ganas"* (groups).

Charaka Samhita describes 600 purgative preparations and 500 decoctions classified into 50 principal groups according to their action (Table I). Some common constituent decoctives keep recurring in these principal groups, the reasons for which are explained thus:

"A single drug may have many appellations owing to its diverse actions. A man is able to perform various actions. He is given that particular appellation which is characteristic of the action which he does, either as an agent or instrument or doer. The same thing is observed in the case of drugs".

It is interesting to see how the ancient physicians classified substances according to the concepts then prevalent, and how their mind worked in making working hypotheses, which look so far removed and irrelevant in today's thinking.

"Substances that are heavy, rough, hard, slow, stable, clear, dense and gross and abounding in the quality of *odour,* pertain to the proto-element *earth.* They promote compactness, plumpness, heaviness and stability".

"Substances that are fluid, unctuous, cold, slow, soft and slimy and abounding in the quality of *taste,* pertain to the proto-element *water.* They produce moisture, unctuousness, union, liquefaction, softness and delight".

"Substances that are hot, acute, subtle, light, dry and clear and abounding in the quality of *form* pertain to the proto-element *fire.* They produce burning, digestion, radiance, lustre and colour".

"Substances that are light, cold, dry, rough, clear and subtle and abounding in the quality of *touch,* pertain to the proto-element *air.* They produce dryness, depression, clearness and lightness".

"Substances that are soft, light, subtle, smooth and abounding in the quality of *sound,* pertain to the proto-element *ether.* They produce softness, porousness and lightness.

"In the light of this knowledge there is in the world no substance that may not be used as medicine in this or that manner, for this or that purpose".

"Whatever therefore substances do, whether by virtue of their nature as substances, or by virtue of their qualities, or by virtue of both their substantive and qualitative nature, in any given time, at any given place, having been administered in a given mode with a given result in view — all that is their *action*. Whereby they act is the *potency*. Wherein they act is the *place*. When they act is the *time*. How they act is the *mode*. What they achieve is the *result*".

"Heavy things increase and light things decrease by the repeated use of heavy and light articles".

"Substances are divided into 63 groups according to the distribution of tastes. This number of 63 swells into an incomputable figure if the after-tastes are taken into count".

"The sweet taste is born of the preponderance of the water element, the sour taste is born of the preponderance of the earth and fire elements, the salt taste is born of the preponderance of water and fire elements, the pungent taste is born of the preponderance of the air and fire elements. The bitter taste is born of the preponderance of the air and ether elements; and the astringent taste is born of the preponderance of the air and earth elements".

"Among these, the tastes which are of the nature of fire and air have, for the most part, a tendency to go upwards by virtue of the light and soaring quality of air and the propensity of fire to flame upwards".

"Whereas tastes which are of the nature of water and earth have, for the most part, a tendency to go downwards by virtue of the heavy nature of earth and the propensity of water to flow downwards, the tastes of a mixed nature evince both these tendencies".

The Qualities and Actions of Each Taste

"*Sweet taste* increases the body nutrient fluid, blood, flesh, fat, bone, bone marrow, vital essence and semen, prolongs life, clarifies the sense organs, imparts vigour and complexion, *alleviates pitta, toxicosis* and *vata,* and allays thirst and burning sensation. It promotes cheerfulness, vitality, allays fainting".

At this juncture it is tempting to speculate that the above hypothesis was built on the basis of observing the effects of sugar on hypoglycaemia

brought on by exertion, and the effect of sweet eatables on the healthy people.

"The salt taste is diffusive, it is liquefacient, digestive, curative of 'vata', stiffness, obstruction and accumulations. It gives relish to food and is always used in food''.

Here again one could speculate that the hypothesis could have been built on the basis of observing effects of common salt on salt-depeleted or heat-exhausted subjects (abdominal pain and cramps in the legs attributed to ''vata'', relieved by taking salt) and the effect of potassium salts in paralytic ileus (''curative of obstruction and accumulations''.)

"The bitter taste, though inappetitive, is yet appetising in action. It is *antidotal to poison,* vermicidal, curative of fainting, burning, itching, dermatosis and thirst. It is *febrifuge,* digestive stimulant, depletive and desiccant of moisture''.

Primitive man discovered plant poisons (alkaloids and glycosides) through their bitter taste. He also observed animals vomiting bitter herbs and getting well. By accident he found the willow bark and the cinchona bark reducing fever.

The Nature of Specific Action

''Where there exists similarity in taste, potency and post-digestive changes and yet a difference in action is observed, such special difference in action is called the *specific action of the substance.* For example, white flowered leadwort is pungent in taste and hot in potency. Red physic nut is similar to it in all respects and yet by reason of its specific action it acts as a purgative when administered to man''.

Here is an instance of intuitive wisdom which conceived a *specific effect of a drug,* which would become the dominant theme of 20th century pharmacology.

Ayurvedic physicians considered the *Kala* (duration of action), *Karma* (action), *Veeryaus* (potency), *Adhikaranam* (site of action), *Upaya* (mode of action) and *Phalam* (therapeutic effects) of a drug.

Since the pathogenesis of disease centered on food and digestion, and accumulation of toxic substances in the alimentary tract, the major emphasis was on *emetics* and *purgatives,* a wide variety of which was used. There was also a remarkable preoccupation with cleansing procedures comprising five procedures, *"panch karma",* those including emesis, purgation, enema. Since the concepts about pathology and pathogenesis have now changed considerably, much of the ancient

pharmacopoeia has become irrelevant in the present context. It is interesting to note, however, that iatrogenic illness is not a new phenomenon in the practice of medicine, since Charaka describes twelve complications of improper use of enema — (inadequate action, overaction, exhaustion, distension of abdomen, hiccup, cardiac disorder, diarrhoea, headache, bodyache, griping pain and excessive discharge).

Further Additions to Ayurvedic Pharmacopoeia

It is notable that opium does not figure in the Ayurvedic pharmacopoeia. It was probably added in the 8th century after contact with the Arabic physicians. *"Rasachikitsa"* was added in the 10th century and conceptually it comes closer to modern chemotherapy.

Rise of Modern Pharmacology

The Science of Pharmacology is concerned with the action of drugs or chemicals on the living systems. Today's pharmacology borrows heavily from its sister disciplines such as biochemistry and physiology. Pharmacologists and physiologists speak the same language.

Our understanding of how drugs act depends upon our concepts of how the normal body works. For instance, Ayurveda formed the concept of *Vata* to explain observed phenomena — normal and abnormal. Normal *vata* was responsible for locomotion, speech, sense perception, gastrointestinal mobility, respiration, circulation, and so on. They sought to explain observed abnormal phenomena in terms of disturbed *Vata* — paralysis, tremors, hiccup, vomiting, pain and so on. The effect of drugs was necessarily studied by empiric observations on a large number of patients and beneficial effects, when noticed, were attributed to their qualities in normalising the vitiated *Vata.* The same logic applied to the concept of *pitta* and *kapha.*

The Arabs, best exemplified by Avicenna (980 – 1037 A.D.), made important contributions to the corpus of empiric knowledge about crude herbal drug preparations. Arabic pharmacologists developed Galen's physiology to provide explanations of how the combinations of four qualities of a drug — i.e., hot, cold, moist and dry, could affect the four humours of the body, blood, phlegm, black bile and yellow bile, the Greek humoral concepts similar to Ayurveda. For many centuries this was the language of the pharmacologists.

Twentieth Century biology has brought us a far better understanding of how the normal body works. Today we understand the nature of drug action a lot better than ever before in the history of medicine. As new mechanisms of life processes are elucidated by advances in 20th Century biology, today's attempts to understand drug action are made in terms of cell membrane receptors, activation of membrane-bound adenylate cyclase and cyclic AMP, enzyme activation or inhibition, neuro-transmission and ion fluxes especially of sodium, potassium and calcium, and cell structure as revealed by electron microscopy. Today, in effect a new pharmacology is being mapped out within the interior of the cell. The DNA and RNA, ribosomes, mitochondria, lysosomes, storage granules, micro-tubes are all known sites of drug action. For instance, alkylating agents damage chromosomes and produce mutations by their action on DNA. Streptomycin interferes with normal transcription via messenger RNA; Chloramphenicol binds to ribosomes and inhibits protein synthesis; barbiturates act on mitochondria and inhibit respiration; Corticosteroids protect lysosomal membrances; Colchicin acts on microtubes and stops mitosis at spindle stage.

As in all biological sciences, there is now a tendency to deal with drug effects on a molecular basis. It is interesting to note that conceptually the Ayurvedic physicians were also thinking at a molecular level, so were the Chinese physicians in their concept of *yang* and *yin* which is so similar to current day Cyclic AMP and Cyclic GMP. It is highly rewarding intellectually to follow the march of science from the ancient intuitive approach to the modern experimental approach, a long march spread over 3,000 years. Today's concepts are based on objective documentation of events revealed by, for instance, electron microscopy and autoradiography, and what is more important, they lend themselves to experimental verification and stand the scrutiny of science as enunciated by Karl Popper — testability, verifiability, reproducibility and falsifiability. This is why modern medical science is intellectually more satisfying.

Rise of Chemical Knowledge

In relation to medicine, little knowledge recognizable as chemistry existed prior to the 15th Century. With the rise of alchemy during this period, a limited number of simple and useful chemical compounds became known, for instance, the use of sodium sulphate as a purgative by Johann Rudolph Glauber (1604 – 1688). Paracelsus (1493 – 1541),

an unusual and gifted physician popularised the use of tinctures of salts of potassium, iron and arsenic. His greater contribution was his iconoclastic attitude towards the then prevalent classical Galenical doctrines, which spurred independent thinking.

The first great chemical advance was the isolation in relatively pure chemical form of the active ingredients of crude extracts of plant origin. Friedrich W. Serturner isolated *morphine* from opium in 1806. It took mankind 5,000 years to make this all-important advance. The exact chemical structure of morphine was arrived at in 1923. And the complete synthesis, as a conclusive proof of structure, was achieved in 1950. Today hundreds of synthetic and some semi-synthetic morphine congeners adorn the shelves of organic chemists.

Francois Magendie (1783 – 1855) was able to publish in 1821, a medical formulary made up entirely of purified chemical agents. In it were such alkaloids as emetine from ipecacuanha, quinine from cinchona bark and strychnine from nux vomica.

The industrial revolution of the 19th Century which gave birth to synthetic organic chemistry for industrial use, established the type of knowledge necessary for the synthesis of new drugs. The new chemical industry produced general anaesthetics, disinfectants, antipyretics and hypnotics. Emil Fischer (1852 – 1919) was the great genius of organic synthesis. He collaborated with Joseph von Mering in 1903 in the synthesis of barbital, the first barbiturate. This opened the way for other investigators to synthesize thousands of similar structures. The synthesis of rubber, plastics, commercial solvents, industrial enzymes and synthetic fibres, to mention only a few, have all aided in the eternal quest of new drugs. During the last 25 years, more new drugs have been introduced than all the drugs already existent in the pharmacopoeia put together. Not only are drugs being discovered at an ever increasing rate, but the quantity manufactured and deployed for various purposes is also increasing enormously.

Drugs and Cell Membrane

The use of ether as a general anaesthetic started with the dramatic demonstration given by William Morton, while he was still a medical student at Massachusetts General Hospital in Boston, USA, in 1846. General anaesthesia, which radically altered the surgical scene was a major landmark in the history of medicine.

Sir James Young Simpson and his colleagues in England introduced chloroform in 1847, just twelve months after Morton's use of ether in America.

Although nitrous oxide was prepared in 1772 by Joseph Priestley one year after his discovery of oxygen in Britain, the use of nitrous oxide along with oxygen was introduced by Edmund W. Andrews, a surgeon in Chicago in 1868, in surgery and dentistry.

The understanding about the mode of action of these compounds came much later. In 1899, the German pharmacologists Overton and Meyer observed independently that substances which were common nutrients (such as sugars and amino-acids) did not penetrate readily into cells whereas alcohols, ethers, amides, ketones and various hydrocarbons entered rapidly and produced a narcotic effect (Greek narcosis means numbness). Cells that were active and motile rapidly became inactive on exposure to these agents; when they were removed, the cells promptly recovered. In seeking an explanation for this unexpected difference in the penetration of molecules, Overton suggested that entry of foreign molecules depends on a *physical property* which was common to them all, namely *solubility in lipids,* and that the entry of nutrient molecules required the cells to perform work as in glandular secretion.

The work of Overton and Meyer had important consequences. It led to the view, first, that lipids might be constituents of cell membranes, and second, that the entry of nutrient molecules depended on some form of *active transport;* third, that lipid-solubility was a clue to the mode of action of narcosis-producing drugs.

Recently it has been suggested that narcosis occurs when a constant fraction of a highly polar non-aqueous phase of the cell is occupied by molecules of the narcotic. The greater potency of halothane (CF_3 CHClBr) as compared to chloroform ($CHCl_3$) may be due to its greater volume and mass. Such molecules might, by obstructing aqueous channels in the membrane, interfere with the movements of sodium ions.

The action of polar narcotics (soluble in water as well as in lipids) such as ethyl alcohol which are *metabolized* by the cell is different from the inert gases and the non-polar narcotics such as ether and chloroform which leave the cell unchanged. Probably the action of the latter is readily explicable in *biophysical* terms. There is no evidence so far of their combining with any receptors or inhibiting any enzyme systems.

The Concept of Specific Receptors

In the early years of the 20th Century, a number of synthetic drugs became available for the treatment of some infections, notably syphilis

and trypanosomiasis. Paul Ehrlich (1854 – 1915) developed the concept that the specific effects of a drug could be explained by the reaction between the drug and a particular chemical group in the cell or tissue, a *specific receptor.*

That drugs may work upon only one organ system or may have a highly selective site of action was known to Ayurvedic physicians as shown earlier in this Chapter.

Felice Fontana (1720 – 1805) in 1765, made an exhaustive study of snake venoms and other toxic substances and concluded that drugs act preferentially on one type of body tissue.

James Black (1815 – 1893) using mainly inorganic compounds, established that drugs are active only when they reach a responsive tissue. Comparable studies were made later by A. Crum Brown (1838 – 1923) and T.R. Fraser (1841 – 1920) on organic compounds.

Ehrlich's concept of specific receptors had far reaching consequences, as we shall see later. Receptor theory is an important part of present day pharmacology. It is particularly applicable to drugs which modify behaviour of excitable tissues.

Pharmacodynamics

During the early decades of the 19th century, in France, physiology first developed its scientific identity as an autonomous discipline. Francois Magendie (1783 – 1855) was the pioneer in the development of experimental physiology and the beginnings of experimental pharmacology.

Towards the end of the 19th Century, as the young field of physiology began to emerge, the newly discovered mechanisms of bodily function lent themselves admirably to the description and elucidation of the mode of action of drugs on living organisms. In fact, it is fair to state that the fathers of modern pharmacology were trained primarily in physiology.

Rudolf Buchheim (1820 – 1879) was such a physiologist who became the first recognized professor of pharmacology in 1846. He made many contributions to the study of drug action especially concerning atropine and ergot.

Among the pupils of Buchheim was Oswald Schmiederberg (1838 – 1921) who was destined to establish a long lineage of pharmacologists.

For centuries it was known that eating *ergot,* a fungus infecting rye grains, caused abortion and it was used for inducing labour. it was also

known that eating bread made of infected rye for any considerable time could produce severe gangrene of the limbs. Henry Dale (1875 – 1968), a young man freshly trained by the great physiologists of the day at Cambridge in England brought modern pharmacological science to ergot at the beginning of the 20th Century, with extraordinary success. In 1906, Dale discovered that ergot extract could annul the blood-pressure-raising effect of adrenaline. Dale found that his ergot extract was a partial or selective antagonist to adrenaline; the *excitatory actions* (faster heart rate, higher blood pressure) were reduced but the *inhibitory actions* (bowel, bladder muscle inhibited into quiescence) were left untouched. Dale went on to look at the chemical nature of his ergot extract. *Ergotoxine* was the name given to the "pure" substance found in it. Ergotoxine is now known to be a mixture of three different but closely related substances, all derivatives of lysergic acid.

But the sympatholytic actions, mentioned above, were not the basis of ergot's stimulant action on the uterus. Dale had to wait nearly thirty years to see the agent responsible for this effect, another related derivative of lysergic acid, *ergometrine* (ergonovine) to be extracted from ergot.

Dale discovered two other substances which led to a revolution in pharmacology. Unlike the ergot alkaloids which are complex chemicals, these new substances, *histamine* and *acetylcholine* were very simple substances. Dale showed that histamine acted on tissues and organs throughout the body to produce a picture almost identical with what clinicians later recognized as anaphylactic shock. Histamine opens up millions of pores in the blood capillary walls to flood the area with plasma proteins and blood cells, designed to repel foreign invaders, but as in every war, there are innocent victims: in this case there is also stimulation of the secretions in eyes and nose, contraction of muscles in the bronchi, narrowing the airway, and dilation of blood vessels leading to fall of blood pressure and shock. The whole reaction can be unpleasant, dangerous or even fatal.

The understanding of the pathology produced by histamine led to the development of anti-histaminic drugs in much the same way as ergotoxine blocked some of the effects of adrenaline.

Dale discovered that acetylcholine had two distinct types of action. One type was capable of being blocked by atropine and the other type by nicotine. Indeed, Dale had a central role in establishing the chemical theory of transmission of the nerve impulse. When impulses travel along the nerve fibres which pass between the brain and the muscles,

they release at the nerve endings, the contents of millions of tiny vesicles, each of them containing a few thousand molecules of acetylcholine. These molecules of acetylcholine convey the information from nerve-endings to muscle fibre and initiate its contraction. Drugs having actions like nicotine, including the arrow poison *curare*, can annul this action of acetylcholine and produce muscle paralysis. However, when acetylcholine is released at nerve endings in certain organs such as the heart and blood vessels, atropine, but not curare, is able to block this action.

How does it come about that drugs can pick and choose in this way? How is it that foreign susbtances can produce such selective actions? Twentieth Century molecular biology has given answers to these questions in terms of cell membrane receptors, enzymes and activated proteins.

Drugs and Enzymes

The discovery that enzymes were sensitive to drugs marked the beginning of biochemical pharmacology. In receptor theory the interaction between drug and receptor is analogous to that between substrate and enzyme.

Acetylcholine is an ester which can be rapidly broken down to acetic acid and choline by the catalytic enzyme cholinesterase. At the nerve-muscle junction, as soon as the muscle is stimulated by acetylcholine, the enzyme cholinesterase rapidly destroys it. If the enzyme is inhibited, the effects of the nerve impulses become greatly exaggerated and the muscles are thrown into irregular twitching and spasm.

Physostigmine (Eserine), an alkaloid extracted from the calabar bean, an ordeal poison once used by witch doctors in West Africa, inhibits cholinesterase — a classical example of an enzyme inhibitor. Eserine was the first drug to be used as a *biochemical tool* for the identification of a substrate (acetylcholine) which would otherwise have been destroyed instantly. But for eserine, the theory of neuro-chemical transmission of nerve impulse might have remained untested by experiment.

The so-called nerve gases (contemplated in warfare) are capable of forming *irreversible* chemical bonds with cholinesterase. Other cholinesterase inhibitors like malathion are used as insecticides.

Myasthenia gravis is a disease in which the patient suffers from muscle weakness which is often severe. The muscles behave as though there was not enought acetylcholine to stimulate them. When cholinesterase is *reversibly inhibited* by a drug like neostigmine (which is in the same category as physostigmine) muscle power returns dramatically

because acetylcholine now stays around longer to give stimulation to the muscles.

Many useful drugs are enzyme inhibitors. Allopurinol (zyloric) is chemically almost similar to the substrate hypoxanthine, which is acted upon by xanthine oxidase, an enzyme which helps to add an oxygen molecule to hypoxanthine to produce uric acid. Allopurinol has affinity for the active site of xanthine oxidase, and thus causes *enzyme blockade,* thereby preventing the rise of uric acid and an attack of gout. The unoxidised precursors xanthine and hypoxanthine now accumulate in the tissues and blood but they are readily eliminated by the kidneys into urine.

Drugs can be used to play tricks on enzymes. The enzyme is offered a drug which closely resembles the substrate (which it unites or divides), and the enzyme can be persuaded to make *counterfeit molecules.* For example, noradrenaline, the transmitter at the sympathetic nerve endings, is synthesized from an earlier amino-acid precursor, DOPA. The enzyme DOPA oxidase can also act on administered methyl DOPA to produce methylnoradrenaline which has been described as a *false transmitter* because it is far less effective than the normal neurotransmitter. Methyl DOPA is therefore successful in reducing high blood pressure by decreasing the normal vasoconstrictive effect of noradrenaline.

Cell-Membrane Bound Enzymes and Drugs

Most enzymes are not found free in cell fluid but are firmly fixed to cell membranes. There may be several ranks of enzymes so arranged that the products of one reaction immediately become the substrate for the next. Cell membranes are highly specialized structures made of a mosaic of proteins and fats (lipoproteins) and the movement of molecules and ions across the membrane is strictly regulated. Impedance to the flow of ions gives cell membranes a static charge like an electrified perimeter fence which can be switched on and off as pores in the membrane are opened or closed. This is the mechanism by which cells are sensitive to changes in their environment, the basis of their excitability. Thus specialized junctions between cells, as in the nervous system, heart, smooth and skeletal muscle are highly permeable structures with conductance for ions far greater than in non-junctional membranes. Each heart beat is preceded by a regulated switching off of the cell membrane voltages and the synchronised voltage changes can be detected on the surface of the body with an electrocardiogram.

Some drugs used in the treatment of cardiac rhythm disturbances, selectively act on the junctional cell membranes, particularly of the heart, to alter the flux of ion currents across cell membranes.

In 1914, Wenckebach, a Dutch physician was told by a sailor that when he took quinine for his malarial fever, his palpitation of the heart disappeared. Wenckebach confirmed the effect of quinine, and later its more effective optical isomer quinidine on atrial fibrillation and other cardiac arrhythmias. By a direct action on the conducting cardiac tissue quinidine decreases the velocity of conduction in atria, AV node and ventricles and reduces their excitability. It prolongs the functional refractory period of myocardial cells by slowing depolarization, without affecting the half-time for repolarization which determines the absolute refractory period. The cellular mechanisms for these electrophysiological effects are not well understood. It probably chelates calcium ions, hence the negative inotropic action. It also inhibits ATPase activity and decreases the permeability of cell membrane to sodium ions.

Xylocaine (lidocaine) is another drug which alters the pores through which sodium ions flow into the heart conduction system cells just before each contraction and so can control the speed with which the wave of excitability passes across the heart. Procaine prevents conduction in nerve axons by blocking channels for the entry of sodium ions. By contrast, cardiac glycosides interfere with outward movement of sodium ions from cells and at the same time reduce the entry of potassium, when this is linked to the extrusion of sodium ions. This action of cardiac glycosides is seen not only in junctional membranes of nerve and muscle, but also in red blood cells, the gastric mucosa and renal tubules. The effect may be metabolic since the glycosides influence the activity of ATPase, an enzyme which is normally activated by Na^+, K^+ and Ca^{++}. Thus the actions of cardiac glycosides have been related to such biochemical concepts as the metabolically driven Na^+ pump and the role of calcium ions in the coupling of excitation with contraction in cardiac muscle. Digoxin produces an increased uptake of cell Ca^{++} and this probably facilitates the association between actin and myosin and the contractile process, through Ca^{++} ATPase.

Membrane Transport and Drugs

All cell membranes restrict the movement of other molecules into and out of the cells and there are special arrangements to restrict the

penetration of substances between the blood and the brain, or between the placenta and the fetus. To compensate for this, cell membranes are supplied with special chemical pumps or transport processes to move particularly valuable substances either way across the membranes. Regulated penetration is particularly important in the kidneys. The renal tubules have highly developed systems of transport processes located in their membranes and they actively pick out and return to the blood the molecules that the body needs such as glucose and amino acids, and leave behind the useless end products of metabolism such as urea and uric acid.

Many drugs influence transport in the cells with special functions such as the nephrons. Organic mercurial compounds and drugs containing the sulphonamyl group (SO_2NH_2), notably acetazolamide, inhibit the reabsorption of filtered sodium, whereas aldosterone and corticosterone increase sodium reabsorption. The glycoside phloridzin blocks the reabsorption of glucose in the renal tubules as well as its absorption from the intestines. Vasopressin does not affect the transport of solutes but increases, by a highly selective action, the permeability of the renal tubular epithelium to water.

The effects of drugs on the traffic of ions and other solutes in the different regions of the renal tubules have far-reaching consequences for acid-base regulation in the body and profoundly influences the action of other drugs. For example, drugs that promote the loss of sodium may also cause loss of potassium and a fall in the body store of potassium, thereby lowering the threshold for the toxic effects of cardiac glycosides.

Penicillin is an organic acid and is eliminated at high speed mainly because it is secreted out of the body into the urine by the tubular cells of the kidney. When it is desired to maintain very high blood levels of penicillin as in subacute bacterial endocarditis, a drug like probenecid (Benemid) is used, which is also an organic acid and competes for the same secretory process as used by penicillin so that the elimination of penicillin is impeded by competition and useful high blood levels are attained.

Drug Receptors and Receptor Blockade

There are probably thousands of chemical regulators in the body. The chemical structure of some of them is known (such as acetylcholine, noradrenaline, histamine) and where they are distributed to all cells in the body by the blood rather than released strictly localized to the site

of action, they are classed as hormones. How does any one cell know what is going on if it is being bombarded by a large number of different regulators? The answer is provided by *specific receptors.* Each chemical regulator has built into its conformation and chemical properties some specific piece of biological information. For that information to be received by a cell the information has to be decoded in the same kind of way that a radio receiver decodes radio waves that it is tuned to receive and no others. A receptor has some similarity to the active site of an enzyme, that is, a macromolecular site which shows chemical complementarity in its spatial arrangement and distribution of electronic charges, to the corresponding hormone. However, whereas at an enzyme, the substrate is chemically altered and the enzyme remains unchanged, at a receptor, the hormone is not altered but the interaction changes the receptor. Changes in the conformation and charge distribution at a receptor then triggers off some predetermined change in cellular activity.

Receptors, like enzymes, are also common sites for drugs to act. After all, both of these sites are designed to be the basis for selective chemical effects in physiology, and if drugs happen to contain enough of the recognizable chemical information, they will be able to deceive the body's own selective machinery. Just as enzyme inhibitors (like allopurinol) are often closely related chemically to the normal substrate, so receptor antagonists are often closely related chemically to the natural hormone. Knowledge about the physiological function of a specified hormone/receptor system can be used to guess what the properties of a new interfering substance (antagonist) might be. There are many examples of this kind of speculation, but here is an example which led to the development of *propranolol.*

The noradrenaline receptors are the special chemical sites on the heart muscle cells which first recognize and combine with noradrenaline and then trigger the changes in cellular enzymes which make the heart beat faster and stronger. Propranolol binds to the ß receptors, and not only by itself fails to trigger the receptor but also blocks noradrenaline from doing so.

The beta-blockers were discovered after it was found that the earlier antagonists, the alpha-blockers were unable to prevent the heart responding to adrenaline. New histamine-blockers were discovered after it was found that the old antihistamines were unable to prevent the glands in the stomach lining which secrete hydrochloric acid, from responding to histamine stimulation. Histamine receptors of two types

have now been identified. The antihistamines (frequently used for allergy) block the H_1 receptors. Cimetidine (tagamet) blocks the H_2 receptors.

Histamine is also present in the brain and along with several other chemicals may have a neurotransmitter function about which we know at present very little. With the help of histamine receptor blockers like cimetidine, there is a chance of knowing more about the role of histamine in brain function.

As we understand more and more how drugs make use of the body's own control machinery — receptors, hormones, transport systems, binding sites and so on — to produce selective action, we become interested in more and more varieties of configurations of molecules (derived from plant or animal origin) which might lead to the discovery of newer receptors and scope for newer drugs. Opiate receptors and amphetamine receptors in the brain are recent examples.

Interaction between a drug and its elective site of action is determined by its *goodness of fit* for the active site plus the likelihood that random molecular motion will bring a molecule into contact with that site. The likelihood of such a molecular encounter is mainly determined by the concentration of the molecules. Where a molecular species has high affinity for a site, a low conentration of molecules will achieve effective interaction. But as concentration is increased, effective interaction may begin to take place at lower affinity sites, and new actions, perhaps unwanted and even damaging ones, can occur. This will be true whether the molecule is a natural one (say a hormone) or a foreign one (a drug). For example, a polypeptide hormone secreted by the posterior pituitary regulates the body water content by controlling its reabsorption by the distal renal tubular cells. If however, large unphysiological doses are given intravenously, a new action, vasoconstriction, appears. The latter action was discovered first, hence the hormone was called *vasopressin.* The action on renal tubules was discovered much later and is now called the *antidiuretic hormone.* All kinds of hormones and chemical regulators in the human body such as insulin, histamine and vitamin D can be lethal when used as drugs and given in overdose.

The Adenylate Cyclase System

Cyclic 3-5 adenosine monophosphate (c AMP) acts as an intracellular "second messenger" for a diverse array of peptide hormones and biogenic amines, drugs and toxins. Many hormones (ACTH, MSH,

Calcitonin, parathyroid hormone, FSH, LH, HCG, TSH, TRH, vasopressin, glucagon, beta-adrenergic catecholamines, prostacyclin and prostaglandin E_1) initiate their action by binding to specific receptors on the external surface of the plasma membrane. The hormone-receptor complex activates the membrane-bound enzyme adenylate cyclase which synthesizes cyclic AMP from intracellular ATP. Within the cell, c AMP relays the hormonal message by combining with its own receptor, cAMP-dependent protein kinase. Activated by cAMP, protein kinase transfers the terminal phosphate of ATP to specific protein substrates (usually enzymes). Phosphorylation of these enzymes enhances (or in some cases inhibits) their catalytic activities. Altered activities of these enzymes produce characteristic effects of the hormone on its target cell. An example is glucagon-mediated activation of hepatic phosphorylase and subsequent release of millions of glucose molecules from glycogen from each single liver cell.

Each of the protein molecules involved in the intricate "pull-push" mechanisms which increase or decrease or turn off the synthesis, intracellular accumulation and action of the second messenger, represents a potential site for regulation of hormonal responsiveness, for therapeutic and toxic actions of drugs and for pathological alterations in disease.

Cyclic AMP provides a simple, economical and highly specific way of communicating diverse and complex messages.

Several pharmacological antagonists act by blocking the binding of neurotransmitters and hormones to their specific receptors e.g., propranolol at beta-adrenergic receptors and cimetidine at H_2 – histamine receptors. The therapeutic action of these agents depends upon elevations or decrease in c AMP content of target cells and tissues in patients. In addition, the methylxanthines, (caffeine & theophylline) block cyclic nucleotide phosphodiesterases and may produce some of their therapeutic effects (e.g., bronchodilation in asthma) by elevating cellular cAMP.

At present cAMP provides an important tool in understanding normal and pathological regulation and in developing new drugs. Adenylate cyclase assays are now routinely used to screen new compounds for their ability to stimulate or block adrenergic, histaminergic and many peptide receptors. Hormone receptors are not the only critical and specific control points in regulation mediated by cyclic AMP. Possibly other proteins (like nucleotide-binding N protein) will

serve as targets of useful therapeutic agents in the future.

Discovery of New Drugs

Discovery of new drugs has been mainly a matter of chance (serendipity), and accident. Of course, it needed observant persons who could notice the unpredicted or the unexpected, draw the right conclusions from the chance or accidental happenings. In the 20th Century drug research has become a planned and deliberate effort, although chance and good luck still play their part. The modern synthetic chemist can reproduce in the test tube substances known in nature; he can also make modifications of the existing structure, or make completely new substances that have never existed before. The design of such chemicals is actuated by the knowledge already acquired about basic physiology and biochemistry of the living cell.

The "screening" programme for testing new drugs begins with animal experiments. The greatest difficulty for the laboratory pharmacologist lies in designing his animal experiments to yield the maximum information from a relatively few animals and to be relevant to human physiology and pathology. Random screening approach uses a whole battery of different animal tests. In this several doses of the compound to be tested are given to groups of mice and their behaviour is monitored by trained observers, or automatic apparatus. Heart and respiratory rates, temperature, body activity etc., are recorded and compared with undosed control groups. All changes or lack of change are registered on special form or fed into a computer which provides a "profile of activity". This profile is examined and compared with the profiles of standard drugs. Observers must always be kept ignorant of what the animals have received, to avoid their bias. Sedatives, hypnotics, tranquillizers, psychic stimulants, muscle relaxants, analgesic, convulsant, neuromuscular-blocking, atropine-like, ganglion-blocking, sympathomimetic, antipyretic, vasodilator acetylcholine-like drugs can be detected by this approach.

Any such screening test is a compromise based on the need for simplicity and speed and the sensitivity in detection of useful drugs. No one knows whether more valuable drugs have been missed than have been found.

Any compound which shows some promise in the "primary random screen" is then subjected to more detailed pharmacological and biochemical study devised in the light of the initial results. Either

whole animals or isolated tissues may be used. Several species of animals will be used, generally mice, rats, cats and dogs and sometimes guinea pigs and rabbits.

Many experimental disease models are used for screening of drugs, such as high blood pressure, peptic ulcer, arthritis, convulsions. These diseases may be induced in those animals or there may be available spontaneous disease models in animals, like the New Zealand Black mice with an autoimmune disease similar to the human disease SLE (systemic lupus erythematosus).

A great deal of imaginative skill and experience is used by the medicinal chemist when he moves from a parent compound to make chemical variants. A cycle of chemical modification, screening test, evaluation and then a new chemical modification will usually lead to new drugs which are more active, less toxic, or easier to use than the original one.

As well as testing the effects of graded single doses, chronic pharmacologic studies are sometimes needed for drugs can not only alter some bodily functions acutely, but also alter some others more slowly. Many drugs are now given to human beings for many years such as the anti-hypertensive drugs, tranquillizers & oral contraceptives.

Animal studies give valuable information about pharmacokinetics (absorption, distribution, elimination). Whole body autoradiography using H-3 (tritium) labelled drugs has provided a valuable method of studying drug distribution, and hence prediction of its effects.

Pharmacological studies are integrated with toxicological studies to get a complete picture of the unwanted as well as the wanted drug effects. Some information on toxicity will generally be obtained during the initial pharmacologic testing, which is extended by the special toxicologic investigations. Acute toxicity testing is done to establish the ratio between the maximum tolerated dose and minimum curative dose to give some indication of the safety in relation to efficacy. The usual method of calculating toxicity is the ratio LD50/ED50 i.e., the dose that is lethal to 50 per cent of the animals (LD50) divided by the dose that has the desired effect in 50 per cent of the animals(ED50).

It is more important to know how the compound acts as a poison. This may need biochemical studies and microscopic studies with repeated or long-term administration of the drug. Subacute (short term upto one week) and chronic (long term, even life-long) toxicity studies will differ widely according to whether a drug may be needed

to be given once or a few times (for instance, a general anaesthetic) or continuously for years (for instance in epilepsy).

Generally, a drug is given daily and the appearance, activity, food intake, growth and reproductive ability in groups of animals on different doses are observed. Biochemical studies (urine, blood etc.) are commonly done and microscopic examination of most tissues, especially the liver, kidneys and bone marrow are done in animals that die as well as in sample animals killed at intervals during the test.

There are special problems of testing for adverse effects on the fetus and for carcinogenesis or genetic changes.

As knowledge of basic mechanism advances it may become routine to use tissue cultures to predict what effects a drug will have in man but till that happens, animals will have to be used. A dominant problem is that of predicting from experiments with chemicals on animals what effects these chemicals will have in man. Failures of prediction will occur from time to time (e.g., Thalidomide disaster) although, with growth of adequate systems for monitoring possible adverse reactions it should be on a much smaller scale.

Proper Perspective about Safety of Drugs

For the alarmists who have exaggerated the risks of modern drugs, the following figures on the general safety of drugs in relation to accidents and to smoking in Britain (population 57 million) in one recent year will have a sobering effect:

Deaths due to drug adverse effects	43
" " " accidents to children	1700
" " " motor vehicle accidents	7084
" " " accidents in the home	6000
" " " lung cancer, largely due to smoking	28252

Introduction of New Drugs

Rational clinical introduction of a potential new drug requires study in four successive stages:

1. The pharmacodynamics (effect of the drug on the body) and the pharmacokinetics (absorption, distribution, metabolism and excretion) in healthy human volunteers or patients often in a special clinical pharmacology laboratory.

2. Wider use on patients to establish potential therapeutic utility, dosage schedule and some notion of common adverse effects.

3. Formal assessment of its therapeutic merits, compared with those of other remedies, when these exist.

4. Monitoring for adverse reactions as well as therapeutic benefits after general release..

Since testing new drugs on volunteers as well as patients raise ethical questions, it is now mandatory in all countries to subject all such projects to formal ethical review by an independent committee comprising medical, nursing, legal and lay members. Furthermore "informed consent" has to be obtained from the patients or healthy volunteers who agree to participate in the clinical trials.

The emergence of *clinical pharmacology* in the last quarter century as a special sub-speciality was a response to a pressing need for clinical scientists qualified to test the effects of new drugs and to design suitable trials in human beings. Critical clinical pharmacology of Ayurvedic drugs has been carried out in India by several investigators. I will give a brief review of the utility of such efforts and also indicate what directions such efforts in future would take. Table II gives a list of popular Ayurvedic drugs whose scientific validation may be taken up immediately.

20th Century Look at Ayurvedic Pharmacopoeia

In 1908, Dr. K. M. Nadkarni published "The Indian Materia Medica". In 1918 Dr. Kirtikar and Basu published in two volumes, "The Indian Medicinal Plants". In 1923 Sir Ramnath Chopra began work on a large number of plant extracts in experimental animals. The animals used for screening have been dogs, rabbits and rats. In 1955, Chopra & Chopra published a review of Indian Medicinal plants.

Biological evaluation of plant material presents some uncontrolled and complex problems. Phytoconstituents are known to vary depending upon climate, soil, humidity, harvesting, harvesting time etc. Distinct chemical races of plants are known to exist, which vary in their biological activity. The selection of an appropriate solvent method of extraction is of crucial importance. Many solvents are deleterious to essential plant constituents, or may fail to extract the desired active ingredient. The method of extraction is equally important. Volatile materials will be lost in the solvent extraction or in solvent boiling at low temperatures. The presence of antagonistic substances can result in a failure to detect either of the two or more active constituents. Many plants accumulate large quantities of toxic inorganic constituents such as selenium, nitrates, copper, magnesium etc. All of these may produce biological action by themselves, or

interfere with actions of organic constituents present in the plant material. This may lead to a premature abandonment of interest in the plant material.

The most important single event that aroused interest of modern physicians in the Ayurvedic Pharmacopoeia was the published report in the British Heart Journal by Dr. Rustum Jal Vakil in 1949 on the usefulness of Serpina (whole extract of *Sarpagandha* or Rauwolfia Serpentina) in the treatment of hypertension. Its pharmacological properties were earlier investigated by Paranjpe in 1942, and then by Sen and Bose. As we know now, reserpine, the active alkaloid depletes the stores of catecholamines and 5-hydroxytryptamine in the various tissues such as the heart, blood vessels, intestines and adrenal modulla. The catecholamines and 5-HT in the brain are also markedly reduced, thereby producing tranquillization, mental depression and Parkinsonism-like syndrome.

Reserpine gave an impetus to a vigorous search for newer drugs of the same class. The novel and very interesting actions of reserpine heralded a new era in the field of psychopharmacology, and the advent of tranquillizers.

That the possibilities of discovering new gems from Ayurvedic pharmacopoeia are by no means exhausted is shown by yet another recent discovery—Forskolin. The Indian plant Coleus forhlii Briq is mentioned in Nadkarni's Materia Medica. Scientists from Hoechst Pharmaceuticals recently showed Forskolin to be a unique diterpene, which activates adenylatecyclase and cyclic AMP, thereby producing inotropic action on myocardium, increasing the amplitude of contraction of the heart and increasing coronary blood flow. HL 725, a synthetic compound derived from Forskolin is shown to selectively lower peripheral vascular resistance in essential hypertension. HL 725 is shown to inhibit phosphodiesterase in platelets and cardiac muscle, thereby increasing cyclic AMP activity. These examples illustrate the adoption of stereochemistry in response to the clinicians' demands for biologically active compounds.

Professor U. K. Seth has reviewed the literature of 135 indigenous diuretics and clinical & experimental evaluation of 52 plant diuretics. It is obvious that none of them comes anywhere near the effectiveness of modern diuretics. The diuretic activity of watery extracts of *Punarnava* and Gokhru were attributed to their high potassium content. For this reason these herbal remedies, so also coconut water (74 mEq potassium

per litre) would provide a useful adjunct to overcome the undesirable loss of potassium common to many modern diuretics.

In the treatment of rheumatoid arthritis *Guggulu* (Commiphora mukul), *Eranda* (Ricious Communis), *Nirgundi* (Vitex Negundo), *Gourakh* (Dalbergia Lanceolaria) *Rasna* (Pluchea lanceolata), *Gandha Prasarini* (Paederia foetida), *Bala* (Sida humilis) were shown to be significantly effective by Chaturvedi and Singh as anti-inflammatory agents in formaldehyde-induced arthritis in rats. In view of the undesirable side-effects of most modern non-steroidal anti-inflammatory drugs, there is an obvious need for effective remedies or adjuncts for rheumatoid arthritis.

An ICMR-sponsored clinical trial on Ayurvedic treatment of rheumatoid arthritis is going on for the last five years. I am awaiting the publication of their results with great interest, and I must confess, with a lot of skepticism, and reservation. It is unfortunate that persons in high positions make enthusiastic claims without firm data base.

The subject of wound healing, described as *Vrana-Ropana* in *Sushruta Samhita,* continues to evoke current interest. Ropana Drugs are described as the promoters of healing. Deshpande, Pathak and Gode from the post-Graduate Institute of Indian Medicine at Varanasi, have studied the effect of several Ropana drugs on various parameters; biomechanical wound contraction, tensile strength; biochemical-estimation of mucopolysaccharides and collagen; histological and histochemical, and radioisotopic tracer uptakes. *Helianthus annus* or suryamukhi ointment showed significant reduction in total healing period. *Jasmina auriculatum,* as medicated ghee (Jati Ghrita) showed excellent results in different types of ulcers, burns, abscesses and surgical wounds. *Veruonia Ciueria* (Sahadeis) showed uniformly better pattern of wound healing.

Dr. Ashok Vaidya and Vaidya Antarkar have shown in a controlled clinical trial in viral hepatitis that Arogya Vardhini (50 per cent of which is *Picrorrhiza Kurroa)* given in a dose of 750 mg three times daily compared to placebo produces significant fall in serum bilirubin, SGOT and SGPT, apart from reducing symptoms of anorexia, nausea and malaise.

New ways of looking at Ayurvedic drugs

In recent years many Ayurvedic drugs, both herbal and mineral, have been tried in diabetes mellitus, under experimental and clinical conditions. To mention a few: Gymnema Sylvestra, Momordica Charantia,

Tinospora Cordifolia among the herbs and Tribhanga Shila, Shilajit and Jasad Bhasma (Zinc), and Nawajas (mixture of many minerals like zinc, iron, calcium, mica, tin, copper, sulphur, Shilajit etc.) have shown significant results. It is remarkable that unlike insulin or oral hypoglycaemic sulphonylurea compounds, the hypoglycaemic effects of these Ayurvedic drugs are seen in only a small percentage of the diabetic patients. Rather than be disappointed that a particular Ayurvedic drug has been effective in only 20 to 30 per cent of patients, I suggest that we should use these drugs as *pharmacological probes* to unravel the different mechanisms in the diabetic syndrome. If drug A is effective in patient P and not in patient Q, it may well be that two patients represent two different mechanisms of hyperglycaemia. In recent years the IDDM (insulin dependent diabetes mellitus) is seen to have entirely different pathophysiology and clinical course than the NIDDM (non-insulin dependent diabetes mellitus). There is every reason to believe that NIDDM is a mixed bag and various Ayurvedic drugs could serve as pharmacologic probes to further characterise the subgroups of the mixed bag.

Levamisole, the levo-isomer of tetramizole (introduced into veterinary practice in 1966 as a nematocidal drug) has evoked great interest among immunologists. Both in experimental animals and man, levamisole has been shown to be an immunostimulant. It appears to act by restoring cell-mediated immune mechanisms in peripheral leucocytes; precursor T lymphocytes are also stimulated, to differentiate mature T cells (OKT3), helper T cells (OKT4) and suppressor T cells (OKTs). Many Ayurvedic drugs can be evaluated from this angle, since several Ayurvedic drugs have been claimed to be effective in infections and auto-immune disorders.

Bacteria and viruses must attach themselves to specific receptors on target organs. We can think of Ayurvedic drugs in terms of receptor-blocking properties as distinct from bactericidal properties.

Another new area is photochemotherapy, which involves combination of non-ionising electromagnetic radiation like ultraviolet rays and systemically administered photochemically reactive drugs. It has been shown that in the presence of certain naturally occurring tricyclic furocoumarin compounds (psoralens), irradiation with UVR-A (320-400 nanometer) can result in covalent bonding of psoralens to pyrimidine bases in DNA. This photoconjugation may lead to inter-strand cross-linking of psoralen between two base-paired strands of DNA, inhibition of DNA synthesis and cell death. Two hours after oral dose of methoxsalen, UV-A radiation is given for psoriasis.

In vitiligo, methoxsalen plus UV-A treatment can be used in restoring normal skin colour to pigmentless areas. Over 70 per cent of repig-

mentation in vitiligenous areas can be achieved. Over 100 to 200 treatments are needed and this long duration of treatment can be frustrating.

Antarkar and Dr. N. H. Wadia used *Aturagupta (Mucuna pruriens)* in a dose of 15—30 gm per day in 23 cases of Parkinsonism, and found significant improvement on the North Western University Disability Scale and other functional parameters. Mucuna pruriens contains L-Dopa and the cost of treatment is only Rs. 15 per month, with minimal side effects. The main problem is the bulk of the drug to be taken daily. Dose for dose comparison of the activity of Mucuna pruriens with L-DOPA suggested that there might be *other non-DOPA active ingredients.* Recent animal experiments with a Dopa-free fraction of Mucuna prurience has confirmed this additional non-DOPA activity.

These illustrative examples enthuse us to continue the endless search of biologically active compounds for use in therapy. In the wise words of Charaka, "Nothing exists in the realm of thought or experience that cannot be used as a medicine".

TABLE I

50 Categories of Drugs described in Charaka Samhita according to their actions

1. Life Promoters
2. Roborants
3. Revulsives
4. Laxatives
5. Synthesizers
6. Digestive stimulants
7. Promotive of strength
8. Promotive of complextion
9. Promotive of voice
10. Cordials
11. Appetizers
12, Anti-haemorrhoids
13. Curative of dermatosis
14. Anti-pruritic
15. Anti-helminthic
16. Antidotes to poison
17. Galactogogue
18. Galacto-depurants
19. Spermatopoietic
20. Spermato-depurants
21. Adjuvants to oleation
22. Adjuvants to sudation
23. Adjuvants to emesis
24. Adjuvants to purgation
25. Adjuvants to corrective enema
26. Adjuvants to unctuous enema
27. Adjuvants to errhines
28. Anti-emetic
29. Adiposus agents
30. Anti-hiccup
31. Intestinal astringents
32. Fecal pigment restorers
33. Ischuretics
34. Urine pigment restorers
35. Diuretic
36. Bechics
37. Anti-dyspnoea
38. Anti-inflammatory
39. Anti-febrile
40. Acopics
41. Refrigerants
42. Calefacients
43. Anti-urticarial
44. Anodyne
45. Analgesic
46. Haemostatic
47. Sedatives
48. Resuscitative
49. Procreants
50. Rejuvenators.

TABLE II

List of popular Ayurvedic drugs whose scientific validation may be taken up immediately

A. Alimentary System

1. Arogyavardhini
2. Arshaghnavati
3. Bilvadichurna
4. Drakshasava
5. Echabhedi
6. Gandharvaharataki
7. Hingashtaka
8. Jatifaladichurna
9. Kumari Asava
10. Mayurpichhamashi
11. Nagkeshar
12. Sanjeevanvati
13. Samudradichurna
14. Shankhavati
15. Shankhabhasma
16. Shunthichurna
17. Soot Shekhar
18. Suranavatak
19. Triphala

B. Arthritis

1. Dashamularishta
2. Narayan Taila
3. Yogaraj guggula

C. Fever

1. Pravala bhasma
2. Pravala pisti
3. Soot shekhar

D. Dermatology

1. Gandhak Rasayana
2. Gulabi Malhar
3. Haridrakhandayoga
4. Manjishtha
5. Ral malahar
6. Tankana mishrana malahar

E. Respiratory

1. Anu taila
2. Gojiwadiquath
3. Laghumalini
4. Shwarkuthar
5. Yashtimadhuchurna

F. Urinary System

1. Arogyavardhini
2. Chandrapravati
3. Gokshuradigugul
4. Punarnava

G. Gynaec & Obst.

1. Boladivati
2. Dashamularishta
3. Nagkeshar

Chapter 17

TOXICOLOGY, ANCIENT AND MODERN

Introduction

One complete section of the octapartite *Charaka Samhita* is devoted to *"Vishatantra"* or toxicology. Ayurveda recognized poisons of animal and vegetable origin. *Charaka Samhita* lists 21 vegetable poisons and many animal poisons such as serpents, scorpions, insects, spiders, rats, fishes, dogs and so on. Scientists were to learn much later that bacteria, the simplest of free-living organisms, produce some of the most lethal poisons known to man. For instance, *botulinum* toxin and *tetanus* toxin are several million times more toxic than the plant poison strychnine. The human species has had to contend with bacteria and fungi, snakes and scorpions, jellyfish and starfish, sting rays and spiders, and an enormous variety of poisonous plants. The list of poisons furnished ready-made by nature has been extended mightily in recent years by human ingenuity and the chemical industry. Thinkers and environmental and ecological experts are very much concerned with the immediate and long term effects of such chemical poisons like pesticides.

A poison is difficult to define with legalistic rigour. Even pure water is toxic when it is retained by the body in excess, and can kill the patient (water intoxication). Even small quantities of water can cause death when inhaled into the lungs. The accepted pharmacological definition of poison is "any substance that, in relatively very small quantities, can cause illness or death in the living organism by *chemical action.*" No reasonable definition of poison can exclude the thousands of substances which in small doses produce physiological changes which, being used customarily for the treatment of disease, are identified as *drugs.* William Withering, who defined the clinical use of fox glove leaves (digitalis) in heart failure and "dropsy", wrote in 1787: "Poisons in small doses are the best medicines; and useful medicines

in too large doses are poisonous''. That is to say that *drugs are useful poisons,* with *selective toxicity.* In fact pharmacology and toxicology go hand in hand.

Poisons represent a major public health hazard particularly to children. Millions of people all over the world suffer from non-fatal poisoning, a quarter of them being children. There are thousands of fatalities by poisoning for suicidal (and less commonly, homicidal) purpose. The effects of ''socially accepted poisons'' like ethyl alcohol and tobacco are discussed in a different section of this book.

Mechanism of Action of Poisons

''Poisons can be employed as agents of life's destruction or as a means of relief of disease, but for the physiologist poison is an instrument for analysing and understanding the most delicate phenomena of the living machine, and by studying attentively the mechanism of death in diverse types of poisoning he can learn indirectly much about the physiological processes of life''. These words of Claude Bernard written a hundred years ago, still summarise concisely the scientific significance of poisons. Curare, the specific agent that he was discussing, remains one of the best examples of the tripartite nature of this loose category of substances. Curare first came to the attention of scientists as an arrow-poison used by South American Indians to kill game and enemies. Bernard himself first applied it as a physiological scalpel in his pioneering studies of nerve and muscle function. More recently tubocurarine is used as a muscle relaxant during surgical anaesthesia. As Bernard anticipated, poisons have taught us a good deal about the chemistry of living matter. Scientists constantly strive to elucidate the chemical mechanisms by which poisons derange or destroy cells; so far the attempts to reduce toxicity to molecular mechanisms have succeeded in only a few cases.

Drugs and poisons may act at two levels of cellular organization; firstly, on mechanisms that are entirely intracellular, primitive and self-regulating such as those required for *respiration, division* and *growth,* and represented in unicellular organisms; and secondly, on controls that are superimposed on the cell from without, as by neurochemical transmitters and general and local hormones or autacoids. In the multicellular organisms these potent molecules not only control specialized activities within the community of cells but also exercise a continuing influence on the metabolic function of all cells.

The distinction is useful, since many drugs that act on the basic

metabolic functions of the cell are those that inhibit respiration (utilisation of oxygen by cells) and growth and so destroy life. Hence those drugs are all potential poisons in large doses. Such drugs include chemotherapeutic agents which act selectively on organisms parasitic in man and animals, and also pesticides and insecticides and disinfectants.

In contrast are drugs that interfere with the synthesis, storage, release and destruction of neurochemical transmitters, or general or local hormones or which are the pharmacological antagonists of these molecules. In all these instances it can be assumed that the drug acts mainly on enzyme systems that control specialised functions of the cell, and not on the systems that are responsible for survival.

Corrosive Poisons

The corrosive poisons, strong acids and alkalis have the most obvious effects on living matter. By massive destruction of cells, they can produce death from shock, haemorrhage (from the gastro-esophageal lining in ingested poison) or incapacitation of some vital organ. Thus the corrosive gas *phosgene* used in chemical warfare during World War I, reacts with water in the lungs to produce hydrochloric acid, which destroys lung tissue and by its irritant action fills the lungs with fluids. Death ultimately results from asphyxiation.

With most corrosive poisons, however, the mode of action is not so clearly discernible. Concentrated sulphuric acid, for instance, does so many things to the body that its specifically lethal activities are hard to isolate. Moreover, its catastrophic effects on tissue leave little for the physiologist to examine. Some corrosive poisons may produce death simply by shifting the delicate acid-alkaline balance of the body to the point where vital chemical reactions can no longer occur.

Metabolic Poisons

More subtle in their effects are the metabolic poisons that include most of the powerful drugs in the pharmacopoeia, as well as many other chemicals which have no place in medicine. These compounds do not destroy tissue like the corrosive poisons. Many of them produce no visible tissue change whatsoever. Instead, they accomplish their lethal effect by disrupting one or another of the intricate chemical reactions upon which life depends.

Carbon-monoxide is a major constituent of automobile exhaust-gas

and a common agent of suicide in USA. Almost any flame or combustion device emits carbon-monoxide. Its lethal effects are largely attributable to its strong affinity for haemoglobin, the protein in the red blood cells that transports oxygen from the lungs to the tissues. Carbon-monoxide combines with haemoglobin 200 to 300 times more readily than does oxygen. Hence a carbon-monoxide concentration of only 0.5 per cent in the air will convert half the haemoglobin in the blood into carboxyhaemoglobin, a compound that cannot transport oxygen to the tissues. Moreover, the presence of carboxyhaemoglobin alters the properties of normal haemoglobin, so that even the remaining fraction functions with reduced efficiency. The victim undergoes a sort of internal asphyxiation.

The treatment of acute carbon-monoxide poisoning is based on the fact that the association between carbon-monoxide and haemoglobin is reversible. If the victim is removed from the contaminated atmosphere and given pure oxygen to breathe, the carboxyhaemoglobin gradually gives up its carbon-monoxide to yield active haemoglobins. For the same reasons hyperbaric oxygen is helpful in seriously poisoned patients. Transfusion of packed red cells is also of value. Unfortunately a few persons who recover from carbon-monoxide poisoning suffer damage to the vision or to the nervous system that may be permanent.

The cyanide ion is an exceedingly potent and rapid-acting poison. The extreme toxicity of cyanide is due to its ready reaction with the trivalent ion of cytochrome oxidase, an enzyme somewhat similar to haemoglobin, which plays an almost ubiquitous role in cellular respiration. The cyanide ion, introduced into the body in the form of hydrocyanic acid, or its salts, is believed to inactivate cytochrome oxidase somewhat as carbon-monoxide inactivates haemoglobin. Formation of the cytochrome-oxidase-cyanide complex blocks electron transport, thus inhibiting oxygen utilization. This results in cellular dysfunction and death.

Inhalation of hydrogen cyanide may cause death within a minute. Oral dose acts more slowly requiring several minutes for the appearance of symptoms and upto several hours for death. The first effect is an increase in ventilation because of the blockade of oxidative metabolism in the chemoreceptor cells.

The objective of treatment is the production of methaemoglobin by the administration of nitrite. The trivalent ion of methaemoglobin competes with cytochrome oxidase for the cyanide ion. The

cytochrome oxidase-cyanide complex dissociates and enzymatic function and cell respiration are restored. Further detoxification then is achieved by the administration of thiosulphate. Rhodanese, an enzyme with obscure function found in many mammalian tissues catalyzes the reaction of thiosulphate with cyanide liberated by the dissociation of cyanmethaemoglobin. Thiocyanate, which is relatively non-toxic is formed and readily excreted in the urine.

Since speed is of the essence, nitrite should be immediately administered by inhalation of amyl nitrite perles, one every two minutes unless blood pressure is below 80 mm Hg. This is followed as soon as possible, by I.V. injection of 10 ml of 3% sodium nitrite over a 3-minute period. Then 50 ml of 25% sodium thiosulphate should be given I.V. over a 10-minute period.

Toxic Metabolites of Drugs

Paracetamol or acetaminophen has become a popular alternative to salicylates as an analgesic and antipyretic. It is a frequent cause of suicidal poisoning in Britain. While the toxic and lethal dose may vary from patient to patient, hepatic damage may be expected if an adult has taken more than 8 g as a single dose. Hepatic toxicity becomes evident 1 to 2 days after ingestion. There is good evidence that damage to tissue, especially liver is caused by *metabolites* of acetaminophen and not the drug itself. At therapeutic doses acetaminophen is eliminated mainly conjugated to sulphate or glucuronic acid. A small amount of acetaminophen is activated by the cytochrome P450 system and conjugated with the sulphydryl group of glutathione to yield a non-toxic mercapturic acid. After an overdose, the pathway of conjugation to the sulphate and glucuronic acid becomes saturated, an increasing fraction of the drug is activated by the P450 system, glutathione stores are depleted and the reactive intermediaries then become free to bind covalently to liver macromolecules and cause necrosis.

Treatment of acetaminophen poisoning should begin with induction of emesis or gastric lavage followed by the ingestion of activated charcoal. Since endogenous glutathione appears to have a protective effect, several other sulphydryl compounds have been studied for protection against hepatotoxicity. N-acetylcysteine 140 mg/kg, given orally within 10 hours of ingestion of the drug as a loading dose, and a maintenance dose of 70 mg/kg every 4 hours for 3 days, effectively reduces hepatotoxicity.

Chlorinated Insecticides

These compounds are ingredients of insecticide sprays, dusts or solutions. The great majority of these compounds are chlorinated diphenyls (e.g. DDT, TDE, DFDT, DMC, Neotran) or chlorinated polycyclic compounds (e.g. aldrin, chlordane, dieldrin, endrin, heptachlor). Lindane is a hexachlorobenzene. The chlorinated insecticides are soluble in lipids and organic solvents but not in water. They are poorly absorbed unless dissolved in a vehicle such as kerosene, petroleum distillates or other organic solvents. Under these circumstances they readily enter the body through the skin, airways or gut.

The initial symptoms of acute poisoning are nausea, vomiting, headache, dizziness, apprehension, excitement and muscular tremors and weakness, followed by generalized hyperexcitability of the central nervous system leading to delirium, tonic and clonic convulsions followed by progressive depression with paralysis, coma and death. In addition endrin is strongly hepatotoxic.

Cholestyramine accelerates the excretion of chlorinated hydrocarbon chlordecone by preventing reabsorption following biliary excretion, and it may well have similar effects on the excretion of pesticides such as DDT & dieldrin which remain in the body for prolonged periods.

Cholinesterase Inhibitor Insecticides

In agriculture, control of soft-bodied insects is achieved by organic phosphates (e.g. Parathion, Malathion) or by carbamates (e.g. carbaryl, Mactacil).

The toxicity of these agents results from inactivation of acetylcholinesterase which allows accumulation of excessive amounts of acetylcholine at a number of sites: Central nervous system, autonomic ganglia, parasympathetic nerve endings and motor nerve endings.

Toxic muscarine effects include nausea, vomiting, diarrhoea, involuntary defecation and urination, blurring of vision due to miosis, sweating, lacrimation and salivation. Nicotinic effects include muscle twitching fasciculations, weakness and flaccid paralysis. Respiratory depression and coma occur due to central nervous system effects. Cardiac arrhythmias and pulmonary edema as well as EEG abnormalities also occur.

Atropine is the antidote for excessive acetylcholine action on the

central nervous system and parasympathetic nerve endings. A dose of 2 mg is injected intramuscularly and repeated every 10 minutes until parasympathetic manifestations are controlled and signs of atropinisation appear. Atropine is virtually ineffective against autonomic ganglionic actions of acetylcholine and against the peripheral neuromuscular paralysis, whose recovery must await the gradual manufacture of fresh, unpoisoned cholinesterase.

As a fruit of fundamental research into the mechanism by which cholinesterase breaks down acetylcholine, a new antidote has been found. The enzyme cholinesterase has two "active sites" which interact with different parts of the acetylcholine molecule. By attaching itself to these two sites the acetylcholine molecule splits into free choline and an acetyl group (CH_3CO) that remains bound to the enzyme. The acetyl group then reacts with water, forming free acetic acid, and liberating the enzyme for further work.

The organic phosphates, probably by means of the electron-seeking phosphorus atoms which all of them contain, tenaciously pre-empt the site on the cholinesterase molecule that normally accepts the acetyl group. Irwin N. Wilson and David Nachmansohn of the Columbia University College of Physicians and Surgeons were able to devise a compound, pyridine aldoxime methiodide, that can pry the organic phosphate molecule and *reverse* the phosphate-ester bond formed by the organic phosphate at the enzyme active site. *Pralidoxime* is useful in the treatment of organic phosphate cholinesterase inhibition, when given in a dose of 1gm I.V. over a 5-minute period, and repeated every 8 to 12 hours upto 4 times. Energetic therapy with artificial ventilation, atropine and pralidoxime allows survival after doses of organic phosphate esters vastly exceeding the usual fatal dose.

The nerve gases including di-isopropyl-fluorophosphate, tetraethyl-pyrophosphate, irreversibly bind to cholinesterase. Though interest in the nerve gases originally stemmed from their possibilities in chemical warfare, the compounds have yielded an abundant non-military harvest. For example, DFP has helped to unravel the fine structure of several enzymes which, like cholinesterase, bind it tightly at their active sites. Molecules of trypsin and chymotrypsin (the protein digesting enzymes secreted by the exocrine pancreas) can be labelled with DFP containing radioactive phosphorus atoms and then be degraded into small fragments; the labelled fragments identify their active segments of the enzyme molecule.

Botulinum Toxin

The botulinum toxin, an occasional cause of human food poisoning, disrupts the acetylcholine cycle no less efficiently than do the anticholinesterase poisons, but it works in the opposite side of the biochemical cycle. Instead of raising the concentration of acetylcholine, it *lowers* it to paralytic levels. Botulinum toxin binds to the nerve terminal membrane and blocks the calcium-stimulated release of acetylcholine from the vesicles in the terminals. Botulinum toxin has the distinction of being the most poisonous substance yet discovered. A lethal dose for a mouse is as little as 10 – 13ng/kg.

Similar in action to botulinum toxin and almost as deadly is the toxin secreted by the poisonous dinoflagellates. These microscopic marine organisms can kill fish by the millions when they multiply explosively in "red tides". The concentration of their toxin in the digestive tracts of mollusks accounts for many cases of shell-fish poisoning in man.

Mercury Poisoning

In the early 1950's fishermen and their families around Minamata Bay in Japan were stricken with a mysterious neurological illness. The disease produced progressive weakness of the muscles, loss of vision due to visual cortex lesions, impairment of cerebral functions especially cerebellar ataxia, eventual paralysis and in some cases coma and death. It was soon observed that Minamata seabirds and household cats, which like the fisherfolk subsist mainly on fish, showed signs of the same disease. This led to the discovery of high concentrations of mercury compounds in fish and shell-fish taken from the bay, and the source of mercury was traced to the effluent from a factory.

Since then there have been several other alarming incidents in other parts of the world: Iraq, Pakistan, Guatemala, Sweden, North America and Canada. Mankind has become acutely fearful of mercury in the environment. The alarm is understandable; mercury or quicksilver has always been regarded as being magical, in part because of its unique property as the only metal that is a liquid at ordinary temperature. The uncompounded element in liquid form is not a poison; a person could swallow upto a pound or more of quicksilver with no significant adverse effects. Certain compounds of mercury have been used safely for thousands of years. There is evidence that cinnabar or mercuric sulphide (HgS) was mined in China, Asia Minor, the Cyclades and Peru at least two or three millennia ago. Hippocrates is believed to have prescribed mercury sulphide as a medication. By the

Middle Ages, when alchemists had synthesized chlorides, oxides, and various other inorganic compounds and mixtures of mercury, its use in medications began to spread. Calomel (mercurous chloride, HgCl) came into wide use as a cathartic, and in the 16th Century mercury compounds were introduced as a treatment for syphilis.

In agriculture, corrosive sublimate ($HgCl_2$) is used to disinfect seeds and to control many diseases of the tubers, corns and bulbs (including potatoes), and also to protect a number of vegetable crops. Corrosive sublimate is toxic, causing corrosion of the gastro-intestinal tract leading to bloody diarrhoea, injury to the kidneys, ultimately leading to death from renal failure.

What causes concern to environmentalists at present is the alkyl compounds—methyl and ethyl mercurials. The alkyl mercury compounds can cause congenital mental retardation, cerebral palsy and chromosomal abnormalities. The chemical basis for these effects is mercury's strong affinity for sulphur, particularly for the sulphydryl (S-H) groups in proteins (for which arsenic and lead have a similar affinity). Bound to proteins in a cell membrane, the mercury may interfere with a number of enzymes systems essential to cellular metabolism and alter the distribution of ions, change electrical potentials and thus interfere with the movements of fluid across the membrane. There are also indications that binding of mercury to protein disturbs the normal operation of structures, such as mitochondria and lysosomes within the cell.

Research on mercury poisoning in the past has focused primarily on occupational hazards involving prolonged exposure, principally by way of inhalation, for example, among mercury miners and workers in felt hat factories employing mercury nitrate for processing. These exposures are not necessarily incapacitating; they produce tremors, gum inflammation and general irritability. The main threats to which we shall have to give attention now are solid and liquid wastes that may ultimately enter bodies of water, thus threatening fish and eaters of fish, and agricultural uses of mercury that may dangerously contaminate food. We do not yet have enough information to estimate the magnitude of these threats or to establish realistic standards of control. The best way to deal with the problem is to apply the techniques of epidemiology, preventive medicine, public health and industrial hygiene. To implement a control programme, realistic education of the public and legislative action with adequate enforcement will be needed.

Lead Poisoning

Lead has been mined and worked by men for millenniums, because its ductility, high resistance to erosion and other properties make it a very useful metal. The inappropriate use of lead has, however, resulted in outbreaks of lead poisoning in humans from time to time since antiquity. "Plumbism" (from the Latin word for lead) or "Saturnism" (from the alchemical term) was a disease first described by the Greek poet-physician Nicander more than 2000 years ago.

Lead poisoning results from inhalation of fumes as from burning storage batteries, solder, paint spraying or processes that require the remelting of metallic lead. Ingestion of lead-containing material such as paint (especially by children who like its sweetish taste), or water which has stood in lead pipes, illicit whisky contaminated by lead solder in the pipes of stills, have all been responsible for cases of poisoning. Lead is a cumulative poison excreted slowly. Most of the absorbed lead is deposited in the bones; only small amounts are contained in the blood, urine and feces.

Manifestations of lead poisoning are colic, encephalopathy, peripheral neuritis and anaemia. The basis for ill-effects is lead's affinity for S-H groups; due to this interaction S-H groups are not available to certain enzymes that require them. The clearest manifestation of the inhibitory effect of lead on the activity of sulphydryl-dependent enzymes is the disturbance it causes in the biosynthesis of *haem,* the iron-containing constituent that combines with protein (globin) to form haemoglobin, the oxygen-carrying pigment of the red blood cells. Haem is also an essential constituent of the other respiratory pigments, the cytochromes, which play key roles in energy metabolism. The normal pathway for haem synthesis begins with activated succinate (produced by the Kreb's cycle, a major stage in the conversion of food energy to biological energy) and proceeds through a series of steps. Two of these steps are inhibited by lead; two others may also be inhibited, but at higher lead concentrations. Lead is implicated specifically in the metabolism of delta aminolevulinic acid (DALA), catalyzed by the enzyme *ALA dehydrase.*

The functional effect of the metabolic disturbance in the blood is *anaemia.* The metabolism of haem returns to normal and the anaemia improves when the patient is removed from the exposure to lead.

In the kidney, visible changes in the structure of mitochondria are seen under electron microscope; consequently the renal tubular cells

consume more oxygen than normal cells. The damaged tubular cells fail to reabsorb amino-acids, glucose and phosphorus, which are lost in the urine.

In the brain, edema and direct injury to the nerve cells cause lead encephalopathy. In the peripheral nerves, the mitochondria of the Schwann cells are affected, resulting in demyelination and impaired conduction of impulse primarily in the motor nerves of the extremities.

Three highly effective chemicals are now available for the treatment of systemic poisoning with heavy metals by forming non-toxic stable compounds with polyvalent metallic ions, which can be safely excreted in the urine.

The first to be developed was BAL (British anti-leuisite, 2, 3, dimercaptopropanol) which was originally intended as an antidote against the arsenical war gas, leuisite. Its tendency to combine with certain metallic ions such as arsenic, mercury, cobalt, nickel, antimony and gold is so great that it can remove them from combination with the enzyme whose function they impair in the body.

The second antidote to metal poisons is the chelating agent Versene [Ethylenediamine tetra-acetate (EDTA)] which forms cyclic, stable, soluble, non-toxic compounds with most metals. Because Versene reacts with calcium in the same way as with other metals, it must be given as a calcium salt (calcium disodium Versenate) to avoid hypocalcaemia. The material has been used with notable success in lead poisoning (in which BAL by itself is not useful).

Penicillamine (Cuprimine, ß, ß dimethyl-cystine) is an excellent chelating agent for copper, mercury and lead, promotes their excretion in the urine. It may be given orally while the other two antidotes require systemic injection. N-acetyl-di-penicillamine is even more effective than penicillamine in protecting against the effects of mercury.

Cytotoxic Poisons

Amanita phalloides (death cap), Amanita virosa (destroying angel), some other Amanita species, and Galerina Venenata contain heat-stable cyclo-peptide cytotoxins which are rapidly bound to tissues. The principal toxin is α-amanitin which binds to and inhibits specifically the mammalian RNA polymerase responsible for messenger RNA synthesis. Severe cell damage and fatty degeneration may occur in liver, kidneys, striated muscles and brain. Ingestion of these dangerous

mushrooms is followed by a latent period of 6 to 20 hours. Manifestations of cytotoxicity then may appear suddenly and consist of severe nausea, violent abdominal pain, bloody vomiting and diarrhoea, and cardiovascular collapse. The victim may die from acute hepatic neurosis within 4 days.

Poisoning by cytotoxic mushrooms is treated mainly symptomatically.

Venoms, Bites and Stings

Humans have the propensity to come into contact with a great variety of venomous animals. In general, two types of injuries result; those due to the direct effect of venom on the victim, as exemplified in snake bite; and those due to indirect effects of the poison, of which hypersensitivity reaction to bee sting is an example. A third type of injury is described by Charaka — "fear poison".

"When a person bitten by anything in pitch darkness, gets alarmed and suspects a poisonous bite, he develops symptoms of pseudo poison, in the form of fever, vomiting, fainting and burning as well as prostration, stupefaction and diarrhoea. This is regarded as 'fear poison'".

Snake Venoms

The venoms of most species which have been analysed have been found to be mixtures of several toxic proteins and enzymes with diversified and complicated pharmacologic effects. For example, the Indian Cobra (Naja Naja, "*Naga*") contains a neurotoxin, a haemolysin, a cardiotoxin, a cholinesterase, at least three phosphatases, a nucleotidase and a potent inhibitor of cytochrome oxidase. Several venoms including those of the pit vipers contain hyaluronidase and numerous proteolytic enzymes.

The venom of a given species is usually predominantly neurotoxic or necrotising and is frequently associated with haemolysis, blood-clotting abnormalities, alterations in vascular resistance and changes in cardiac dynamics. The venom of elapids including the coral snake, is neurotoxic, with death resulting from respiratory paralysis probably caused by damage to the brain centres and a curariform interference with transmission at the neuromuscular junction. The venom of crotalid snakes produces local tissue injury, haemorrhage and haemolysis; pooling of blood in microcirculation and loss of plasma due to increased capillary permeability cause a marked fall in circulating blood volume and circulatory collapse followed by death.

Systemic absorption of venom occurs through lymphatics, hence therapeutic measures designed to reduce lymphatic function are helpful in controlling symptoms.

Following the bite of a pit viper, severe burning pain develops within a few minutes at the site of the wound. Local swelling rapidly develops and spreads in all directions, accompanied by the appearance of ecchymoses and bullae over the involved area. Serosanguineous fluid oozes from the puncture wounds. Later gangrene of the skin and subcutaneous tissue may develop. Systemic effects include fever, nausea, vomiting, circulatory collapse, pupillary constriction, delirium and convulsions. Death may occur within 6 to 48 hours.

The bite of the coral snake causes little pain and local swelling. There are usually multiple fang marks. Within 10 to 15 minutes numbness and weakness begin in the region of the bite, followed by ataxia, ptosis, pupillary dilatation, palatal and pharyngeal paralysis and slurring of speech. The patient becomes comatose and dies within 8 to 72 hours due to respiratory paralysis.

Cobra bites are painful, often accompanied by severe haemolysis, local necrosis and sloughing in addition to neurotoxic effects.

Treatment of Snake Bite

Charaka Samhita gives the following advice: "In case of a poisonous bite the physician should apply a ligature above the region of the bite and squeeze the part well, before poison has spread in the body, or should try to cut out that part except in the region of the vital organs; or, the physician, filling his mouth with barley-flour or earth must suck up the poison from the bitten area with his mouth".

"The blood is the vehicle of poison as the wind is of fire, so blood must be forced out or congealed by cauterization".

This ancient advice is equally valid today. *Incision and suction are extremely important and should be carried out diligently in every poisonous snake bite.*

Antivenin is the only specific treatment of snake venom poisoning and its use in severe bites is vital. Intravenously administered antivenin leads to the most rapid and effective response. It is a great pity that in our villages many unsubstantiated and useless therapies are practised out of ignorance, thereby delaying antivenin therapy.

Scorpion venom may be fatal to young children or old people, but rarely, healthy adults succumb due to myocarditis. Death usually occurs

within 12 hours but sometimes as late as 48 hours after the sting.

Specific antivenin, reconstituted from lyophilized cat serum is available in USA but has never been available in India.

Hymenoptera venoms (bees, wasps, hornets, yellow jackets and fire ants) contain histamine, various kinins and other vasoactive substances, phospholipases and hyaluronidase. They are haemolytic and neurotoxic in addition to being effective hypersensitizing agents. In hypersentive individuals, a single sting may produce serious anaphylaxis with urticaria, nausea, abdominal or uterine cramps, bronchospasm, massive edema of the face and glottis, dyspnoea, cyanosis, hypotension, coma and death.

Management of Acute Poisoning

Poisoning by chemical agents, accidental, suicidal and criminal, is a common and serious medical problem. In addition to fatal poisoning there is a much greater number of persons who are made seriously ill by poisoning but recover after appropriate therapy. Every effort should be made to avoid accidental poisoning by educating the public in simple preventive measures. All toxic substances should be kept out of the reach of small children. Household chemicals and medicines should be kept in the original containers and all such containers should be labelled. Before taking or administering any medicine one should check the label carefully.

Physicians should always rememeber the protean manifestations of poisoning and maintain a high index of suspicion, in any unexplained illness. Correct treatment of poisoning requires knowledge of both the general principles of management and the details of therapy for specific poisons. Success often depends upon speed of treatment, and when indicated by the clinical situation, several approaches should be used simultaneously. The medical profession can help maintain high standards of therapy by creating and supporting *poison information centres* in cities and towns, to which any physician should have access day and night. Many modern hospitals now have facilities for dialysis which effectively removes many poisons including barbiturates, burate, chlorate, ethanol, glycols, methanol, salicylates, sulphonamides, theophylline and thiocyanate. *Peritoneal dialysis* can be performed easily in any hospital and may be continued for long periods. *Haemo-dialysis* is unquestionably a more effective procedure for removing large amounts of dialyzable poisons. For barbiturates dialysance rates of 50-100 ml/minute have been achieved,a rate of 2 to 10 times faster than during

peritoneal dialysis or forced diuresis. Perfusion of blood through activated charcoal or exchange resin achieves even higher clearance rates than haemodialysis for many poisons. Extracorporeal dialysis and haemoperfusion are clearly the procedures of choice for the rapid removal of poisons from patients who have absorbed amounts which make survival unlikely even under the best supportive care.

The removal of some poisons is accelerated by chemical interaction with other substances followed by renal excretion.

Table I gives an outline of modern treatment of acute poisoning by chemicals. Supportive therapy is crucial even when an antidote is available, to maintain vital functions.

Incidentally, this Table also illustrates the scientific basis of modern therapy, which is intellectually very satisfying.

TABLE I

Treatment of Acute Chemical Poisoning

I. **Prevention of further absorption of poison**
  - A. Poisoning by ingestion
    1. Emptying the stomach
       a. induction of vomiting
       b. gastric lavage.
    2. Minimising gastrointestinal absorption
       a. absorption by activated charcoal
       b. catharsis.
  - B. Poisoning by other routes
    1. Skin — wash with soap and water
    2. Bite or injection site — proximal torniquet application of cold to site
    3. Inhalation — Remove to clean air—Protective mask.

II. Removal of absorbed poisons from body
  - A. Detoxification — enzyme induction
  - B. Biliary excretion — interruption of enterohepatic circulation
  - C. Urinary excretion
    1. Forced diuresis
    2. Alteration of urinary pH
  - D. Dialysis
    1. Peritoneal dialysis
    2. Haemodialysis
  - E. Charcoal or resin haemoperfusion
  - F. Exchange transfusion
  - G. Chelation and chemical binding

III. Supportive therapy

Meticulous nursing care and close observation
Anti-convulsant drugs — diazepam, phenytoin I.V.
Reducing cerebral edema — corticosteroids, mannitol I.V.
Maintenance of ventilation and circulation
Maintenance of fluid and electrolyte & acid base balance.

IV. Administration of systemic antidotes

A. Chemical agents which help reduce the concentration of toxic substances, by

1. combining with the poison
   EDTA with lead
   BAL with mercury
   Penicillamine for copper, lead, mercury
   SH-containing reagents with toxic metabolites of acetaminophen.
2. increasing excretion of the poison
   Chloride or mercurial diuretics in bromide poisoning

B. Pharmacological antagonists

compete with poison for its receptor site
atropine with muscarine
naloxone with morphine
physostigmine with anticholinergics like atropine.

C. Anti-venins

Chapter 18

REJUVENATION OF THE ELDERLY

Introduction

The urge to live, the fear of death, the desire for youth, the distaste for old age and the quest of rejuvenation have always interested mankind from antiquity to modern times. Men seek rejuvenation chiefly with the object of reactivating their sexual vigour, and women to restore their youthful beauty. Essentially, all rejuvenation processes are concerned with the prolongation, as far as possible, of the period of greatest maturity between puberty and old age. The subject is connected with longevity (as distinct from senility) since those who are naturally long-lived are thought not merely to live long but to retain their vigour as well. The aim is to add life to years, not merely years to life.

According to Hindu mythology, there has been a progressive decline in human life-span from the Krutayug (400 years), Tretayug (300 years), Dwaparyug (200 years) to Kaliyug (100 years). Ayurveda, according the Charaka, is a science intended to attain long life. "A person who takes suitable diet and practises self-control lives a full span of 100 years or 36,000 nights, without illness". The objective is to attain the fullest survival and even to overcome the handicaps of nature and age. This concept is embodied in *"Rasayana"* (rejuvenation) and *"Vajikarana"* (virilization). Two parts of the octapartite Ayurved are devoted to rejuvenation and virilization. Charaka asserts that even in old age it is possible to regain youth and remain youthful for a very long period. *Charaka Samhita* claims that it is possible by a special course of rejuvenation of six months' duration, to transform entirely an aged and diseased body into a fresh and youthful one.

In 1889, Charles Brown-Sequard, at the age of 72 years gave a lecture before the French Society of Biology describing how he had prepared a solution by grinding up testicles of young dogs and guinea

pigs, and after preliminary animal experiments gave himself subcutaneous injections of the solution. He concluded by saying that he had rejuvenated himself by thirty years, and that very day was able to "pay a visit" to his young wife. His lecture created a sensation but the success of his treatment was short-lived. His young wife left him and he died in 1894 of a cerebral haemorrhage.

Claims continue to be made from time to time from all parts of the world about rejuvenation therapy and they find a vast, eager and gullible clientele. Hence it is necessary to examine this subject critically and to sort out facts from fancy.

Limits to Longevity

Approximately 1 in 10,000 persons in developed countries lives beyond 100 years, the authentic record being 114 years. The so-called "increase in life expectancy" figures really reflect progress in elimination of premature deaths specially neonatal mortality. Present-day statistics indicate that under ideal socio-economic conditions mean age of death is not far from *85 years.* Women have a life span about five years longer than men, and about five times as many women as men reach 100 years. There is little evidence that the upper limit of human life-span (110 – 115 years) has been siginificantly altered, nor is there any prospect for such a change.

Many have sought for the secrets of longevity but they remain for the most part hidden. On the other hand, agents for "shortevity" and "dejuvenation" seem to be better understood. It is generally agreed that longevity and vitality have genetic and hereditary factors. There appears to be a definite correlation between the ages reached by parents and the life-expectancy of their children. It is also observed that children of younger mothers live longer. Again, certain countries, because of their climate, air, soil, or water are conducive to longer life.

In experimental animals, three factors are known to affect the life-span — heredity, diet and ionising radiation. Recent reports from the Atom Bomb Casualty Commission reveal that the atom bomb survivors of Hiroshima and Nagasaki (1945) are now showing the signs of ageing at a much earlier age than is usual in Japan.

Changes with age are universal, intrinsic, progressive and deleterious. All cells engage in four basic major activities — the *Production of energy* needed for vital cell processes; *synthesis of proteins,* both structural and enzymatic; maintenance of the chemical and osmotic

homeostasis of the cell; and reproduction or *replication*. The ultimate cause of cell death must involve a derangement of those vital functions at the molecular level. Biological research in ageing received its major impetus with the growth of molecular biology.

Changes due to Ageing

Ayurveda divides human life into: (1) childhood which extends upto the age 16, (2) youth and middle age, which extends from sixteen to sixty (Charaka) or seventy (Sushruta), and exhibits progressively the traits of growth *(vivardhamana,* 16 to 20 years of age), youth *(youvana,* 20 to 30 years), Maturity *(sampoornata,* 30 to 40 years), deterioration *(Parihani,* 40 years onwards) which gradually sets in upto sixty years, (3) old age, "wherein, after 60 to 70 years the body elements, sense organs, strength, energy, manhood, valour, memory, understanding, speech and discrimination begin to decay".

"In old age, the strength and energy of a man dwindle day by day. The organs and virility become weak. The hair turns silvery white, the parched skin looks shrivelled, and marks or dots termed as crow's feet-marks appear. The skin sags down and becomes flabby. The hair begins to fall off. The respiration becomes laboured and painful. The body is worn-out like an old building and shakes with bouts of distressing cough. Such a man is incapable of all acts, and all his bodily functions are imperfect".

Twenty centuries after these words were written, we can now measure and quantitate the changes occurring in human beings due to physiological ageing. Table I gives a list of measurements made pertaining to body composition and anthropometrics, circulatory and respiratory functions, renal functions, endocrine functions, neurologic functions, haemopoietic and immunologic functions, metabolic functions and blood chemistry.

These data have been gathered from several studies that have attempted to characterize normal ageing in humans through cross-sectional or longitudinal assessment of various physiological parameters in groups of healthy volunteers. One type of study is based upon repeated measurements of anthropometric, biomedical, psychological and psycho-social variables in the same subject over a period of many years. Such longitudinal studies are difficult because of the relatively long time-span and mobility of populations in industrial societies. A compromise approach combining cross-sectional and longitudinal techniques is commonly used, in which initial data from cross-sectional

studies are supplemented and corrected by data from longitudinal studies.

The selection of a specific sample population represents another critical aspect of research in ageing. The number of participating individuals, age, sex, socio-economic level, professional and family life history, daily level of physical and mental activity, dietary habits, use of alcohol, tobacco and any drugs taken routinely for therapeutic and other purposes, environmental pollution and so on, have to be considered. Institutional geriatric patient population may not represent the true sample for ageing research since they may represent a high proportion from the lower socio-economic background and correspondingly higher incidence of poor health.

TABLE I

Measurements of Physiologic age in man

HISTORY: Medical, Occupational and Nutritional: Use of Medications, Alcohols and Tobacco.

Body Composition and Anthropometrics

* Total volume, * solids, * lipids, and
* water (by He and tritiated water dilution)
* Exchangeable body sodium (by ^{24}Na dilution)
* Total protoplasmic mass (by whole body ^{40}K counting)
  Body weight
* Stature and stem length
* Diameters and circumferences of head, trunk and limbs
* Grip strength, right and left hands
* Skin fold thickness
* Skin elasticity
* Thickness of cortical bone (from X-ray of hand)

Circulatory and Respiratory Functions

* Systolic and diastolic blood pressure
* Ventricular rate
* Electrocardiogram
* Basal metabolic rate
* Respirations per minute
* Vital capacity: forced and one second

Neurologic Functions (including Sensory)

* Standard neurologic examination
* Electroencephalogram
* Evoked responses: flashing light and auditory stimuli
  Electromyogram
  Optometric examination:
  * Visual acuity
  * Phoria
  * Amplitude of accommodation
    Intraocular pressure
  * Retinal (Photograph)
  * Central Visual fields
  * Flicker fusion frequency
* Auditory acuity: 250-8000 hertz
* Taste threshold

Hematopoietic and Immunologic Functions

Hemoglobin
Hemoglobin fractionation (by electrophoresis)
Erythrocyte and leukocyte count
Total plasma volume
Packed cell volume

Circulatory and Respiratory Functions

Partial pressure of carbon dioxide
* Functional residual capacity of the lungs
* Diffusing capacity of the lungs
* Chest X-ray
* Cardiorespiratory performance during and after exercise

Liver circulation time

Renal Functions

Urinalysis (pH, specific gravity, protein, blood)
Urine culture
* Creatinine clearance
* Tubular reabsorption of phosphate
* Phenolsulfonphthalein excretion

Endocrine Functions

* Glucose tolerance

Plasma insulin content
Protein-bound iodine
Free thyroxine
Rate of excretion of hormone or hormone-metabolites in urine:
* 17-Hydroxycorticosteroids
* 17-Oxysteroid, total and individual components of adrenal and testicular origin

Epinephrine
Norepinephrine
Dopamine

Hematopoietic and Immunologic Functions

Erythrocyte sedimentation rate
* Leukocyte differential

Serologic test for syphilis
* Autoantibody titres

Somatic Cell Genetics

* Ploidy of lymphocytes

Metabolic Function: Blood Chemistry Test

Urea nitrogen
Bilirubin
Uric acid
Creatinine
Phosphorus
Calcium
* Total protein
* Protein fractions (by electrophoresis)
* Cholesterol and cholesterol esters
* Triglyceride
* Lipoproteins and lipoprotein phenotype

Alkaline phosphatase
Creatine phosphokinase
Glutamic pyruvic transaminase
Glutamic Oxaloacetic transaminase
Lactic dehydrogenase
Lactic dehydrogenase isozymes

* *These measurements are now believed to undergo changes associated with normal ageing; other measurements included have been less well investigated across age and may permit differentiation of normal pathologic ageing.*

Biologists define ageing as "the sum total of all changes that occur in a living organism with the passage of time and lead to a decreasing ability to survive stress, functional impairment and death".

Most tissues and organs have a large functional reserve. If the functional capacity at age 30 is taken as 100 per cent (concept of *Sampoornata* in Ayurveda), then there is a measurable decline in nerve conduction velocity (15%), resting metabolic rate (20%), cell water (25%), cardiac output (30%), glomerular filtration rate (40%), vital capacity of lungs (50%), renal plasma flow (70%), maximum voluntary ventilation (80%). It is estimated that on an average 30 brain cells die every minute, so that the human brain which weighs 1,500 grams at age 30,

weighs only 1,360 grams at age 90. The number of fibres in a nerve trunk falls 30% during the same period. Similarly the kidneys lose during this period almost 50% of their functioning units or nephrons, muscle weight and strength fall by about 30%.

When we pass on from the whole human body to the individual cell systems, we encounter 3 systems of cells.

1. Cells of the skin, gut, and formed elements of the blood (RBC, WBC and platelet) are constantly being replaced, and therefore are ever young. The stem cells which are the source of such replicative systems, gradually lengthen their cell cycles and the rate of cell production decreases, in old age.

2. Cells of liver and kidney, replicate in response to partial hepatectomy or nephrectomy at all ages.

3. Cells of the brain and muscle, do not replicate in adult life. However, even cells classified as continuously mitotic do not survive indefinitely (in contrast to cancer cells). Senescence at the cellular level appear to be a universal phenomenon of normal cells.

Ageing at the Cellular Level

Study of the simplest unit of organization, the living cell, permits the study of ageing independent of age-related disease. Research in this area was given a major impetus when human skin fibroblasts were found to have a limited potential for replication, about 50 population doublings under the most favourable conditions (the Hayflick phenomenon). This limit is an inherent property of the cells themselves and not of their environment, since in Hayflick's experiments there was no change in the nutrient medium in which the cells were grown.

The actual number of potential doublings of a given cell in vitro is inversely related to the age of its donor. Werner's syndrome or progeria is a rare disease with a single gene defect causing premature ageing; cells from such a patient manifest far fewer doublings than do cells from age-matched controls.

The genetic apparatus of the cell has been examined for clues to senescence, since altered flow of information at any point in the sequence from DNA to RNA to protein synthesis and degradation could be involved. Somatic mutations in DNA, cumulative errors in formation of RNA, or progressive errors in translation to protein are all theories put forward to explain age-related *"intrinsic"* ageing of cells.

The accumulation of free radicals with age has been linked to activity of superoxide dismutase and this in turn to reduced resistance to injury both intracellular and extracellular.

Equally important is the contribution of *"extrinsic"* factors which regulate cellular function. Those systems under special scrutiny in this regard include the nervous, endocrine and immune systems.

The neurotransmitters, notably dopamine, norepinephrine and serotonin have been the focus of special study in relation to ageing. Parkinson's disease, an age-related degenerative disorder of the nervous system is associated with dopamine deficiency in the striatal nuclei, and can be partially treated by L-DOPA replacement. Furthermore, changes in catecholamine metabolism occur in the normal ageing brain. Changes in central nervous system cholenergic status could account for certain alterations in behaviour and mental function. Agents that enhance brain acetylcholine levels enjoy current vogue in the treatment of dementia.

A well-known age-related decline in endocrine function is ovarian failure at menopause in the female. The endocrine changes in the ageing male are less dramatic and include both a decrease in the mean plasma testosterone level and an increase in mean plasma estrogen (of adrenal origin).

The changes in neurotransmitters, endocrine function and the immune systems with age may be interlinked. For instance, production of a thymic cell hormone may decrease with age and this in turn may be under neuro-endocrine regulation. Decline in thymic function may be responsible for increase in auto-immune disease as well as neoplasia.

Age-related decrements in homeostatic efficiency (glucose, osmolarity, thermo-regulation, circadian rhythms, sleep pattern etc.) may produce morbid symptoms in the elderly especially under conditions of stress and acute illness. When observations are made under basal conditions, little or no change is detected in the "milieu interior" (e.g. fasting blood sugar, acidity and bicarbonate content and pH of the arterial blood). However, when experimentally these conditions are disturbed, the *rate* at which normalcy is restored is much slower in older subjects than in the young.

Theoretical Premise for Rejuvenation

Based on our current understanding of cell injury and its repair, it is theoretically possible to postulate mechanisms which will prevent cell

injury and facilitate its repair, and form the basis of rejuvenation.

Quenching of free radicals: Free radicals are molecular groupings possessing an unpaired electron and thus a strong oxidizing tendency. They occur transiently in oxidation-reduction reactions in the tissues and their reactivity may cause cell damage and ageing. Harman reports prolongation of life in mice by feeding *anti-oxidants* such as ethoxyaquin, 2-mercapto-ethylamine (2MEA), butylated hydroxy-toluene (BHT), cystine hydrochloride, alpha-tocopherol (vitamin E), and ascorbic acid (vitamin C). It is interesting to note that *"amaliki"* (myrobalan) which is a common ingredient of the popular Ayurvedic Rasayanas like Chyavanprash, contains abudant supply of vitamin C.

Membrane stabilizers: Agents that stabilize cellular and sub-cellular membranes and thereby protect and regulate transport across cell membranes and prevent release of DNAase, collagenase and other lysosomal enzymes that may participate in age-associated deteriorative changes, can prolong cell life. Experiments in the fruit fly have shown that various substances that act like membrane stabilizers also prolong life — antihistamines, aspirin, anti-oxidants and several corticosteroids.

Lathyrogens: Cross-linking of collagen in the connective tissue is a cause of ageing, hence agents capable of inhibiting cross-linkage (called lathyrogens) can delay ageing of collagen. Examples of such agents are semicarbamide, ß-amino-proprionitrite, aminoacetonitrite and bis-ß cyano-ethylamine.

Stimulants of RNA Synthesis can be achieved by drugs such as magnesium pemoline, diphenyl hydantoin and procainamide. Prof. Ana Aslan of Bucharest proclaims the virtues of procaine, but clinical trials have been inconclusive.

Immuno Suppressants: Since failure of immunologic surveillance is supposed to lead to progressive proliferation of "forbidden clones" including cancer cells, immuno-suppressive drugs like cyclophosphamide and imuran have been used in experimental animals to prolong life. It is interesting to note that the drug Bhallataka described in Ayurveda contains anti-cancer properties in tissue culture.

Ayurvedic Approach to Rejuvenation

The criterion of ideal health in Ayurveda is the best mood in the working of the body, mind and spirit. Ayurveda defines a *happy* life as well as a *good* life.

"The life of such a man is called happy, as is not afflicted with either bodily or mental ailments, is endowed with youth, strength, virility, reputation, enterprise and boldness befitting his abilities, is actuated in deeds by the continued urge of knowledge, science, the senses and sense objects, is possessed of multifarious and delightful amenities accruing from great wealth, and who can plan as he likes. A life that is contrary to this is deemed unhappy life".

"The life of that man is said to be good who is a well wisher of all creatures, who does not covet other people's goods, who is a teller of truth, who is peace-loving, who acts with deliberation, and is not negligent".

"The mental impulses of greed, fear, anger, melancholy, vanity, hatred, harsh speech and evil thoughts are as injurious to the body as to the mind".

The qualifications of a person suitable for rejuvenation, according to Charaka are as follows: "A man who has fortified himself with resolution and purpose, full of faith and single-mindedness, having cast off all sins of the heart, and cherishing goodwill for all creatures".

"No man who has not rid himself of the evils both of mind and body, beginning with the gross ones, can ever expect to get the benefits resulting from vitalization".

It is obvious from the above statements that a controlled clinical trial of rejuvenation by the Ayurvedic method is not possible, right from the inception — namely the choice of a suitable subject. The much-discussed *"Kaya Kalpa"* of the late Pandit Madan Mohan Malaviya was, according to knowledgeable circles, not a success. To my knowledge, no hard data is published on this subject by any of the Ayurvedic Institutions in the country. This is one of those areas where the claimant cannot prove his claim and the critic cannot disprove it!

Procedure for Vitalization Therapy

"In an area resided in by princes, physicians, the twice-born (Brahmin) communities, saintly men, men of virtuous deeds, free from alarm, salubrious, close to a city, where the necessary appurtenances may be had, one should, having selected a good site, cause a retreat to be built with its face towards either the east or the north. It should be high-roofed and commodious, built in three concentric courts, furnished with narrow ventilators; thick walled, congenial in all weathers; well lighted; pleasing to the mind; proof against noises and other disturbing

agents; untenanted by women, and having physicians, medicines and Brahmins ready at call. Thereafter, during the sun's northern course, in the bright half of the month, when the day and stellar constellations are propitious, the man seeking vitalization enters the retreat, having fortified himself in his resolution and purpose, full of faith and single mindedness having cast off all sins of the heart, cherishing goodwill for all creatures''.

''Therein, being cleansed with the purificatory measures he should undergo the vitalization procedure. After sudation and oleation, he drinks with warm water the powder of chebulic myrobalans, rock salt, emblic myrobalans, gur, sweet flag, embelia, turmeric, long pepper and dry ginger, all of equal parts. He should be given to drink thin barley gruel mixed with ghee, for 3 or 5 or 7 days until his intestines have been purged of all fecal accumulation''.

Details are given for various vitalizer preparations containing 5 groups of ingredients.

Thirty-seven ''infallible'' modes of the application of vitalizers have been given. All the recipes have been backed up a firm assurance of ''a hundred years of youthful life''.

The real message, to my mind, lies in the *Ayurvedic approach, rather than the prescriptions* themselves:

''All ills of the body arise from addiction to faulty diet, irregular times or irregular quantities of meals, overindulgence in food when the stomach has not yet recovered from the last meal, addiction to day sleeping, sex-pleasures and wine-imbibing, persons whose bodies are strained by faulty or inordinate indulgence in exercise, and victims to fear, anger, grief, greed, infatuation and over-work''.

''It is on account of such practices that the muscles become flabby, the joints become loose, the blood becomes decomposed and vitality becomes depleted. One becomes languid and sluggish. Such a man fails to enjoy his full measure of life''.

''Therefore, one should give up the above mentioned unwholesome diet and regimen of life, avail oneself of the vitalizing processes''.

''One who speaks the truth, who is free from anger, who abstains from alcohol and sexual congress, hurts no one, avoids overstrain, is tranquil of heart, fair spoken, is endowed with understanding, diligent in spiritual endeavours, always compassionate, moderate and balanced in his waking and sleeping, devoid of egotism, blameless of conduct,

spiritual in temperament, and attached to elders and men who are believers and self-controlled and devoted to scriptural texts — if one endowed with all these qualities makes use of vitalization therapy, he will reap all the benefits of vitalization".

To borrow an expression from Camus, an optimistic belief in rejuvenation may be the attitude of a fool, but to despair of it is an act of a coward!

Chapter 19

VAJIKARANA OR VIRILIFICATION THERAPY IN AYURVEDA

Introduction

Next to the need for food, water and sleep, the sexual urge is the most powerful biological drive. This dominant sex instinct, so essential to the survival of the species, is one of the mainsprings of human motivation, and its fulfilment or frustration is closely bound up with human happiness or misery. The importance of this aspect of human life is duly recognised by Charaka by assigning a complete section of the *Charaka Samhita* to *"Vajikarana"* or virilification. According to Charaka, "It is a therapy which enables one to approach women in an unfrustrated manner, endowing him with great strength and robustness, like that of a stallion, makes one greatly endearing to women, increases one's proportions and strength, causes the seminal secretion even of the aging to remain undiminished and fertile, and enables a man to have many and excellent offsprings".

"The man of self-restraint should seek, always to maintain his virility by means of virilification, as righteousness, wealth, affection and good repute are dependent on the maintenance of healthy manhood".

According to Charaka, the best agent of virilification is an exhilarating sexual partner in the wife. "When the desired sense objects yield great pleasure even if singly experienced by the senses, then what need be said of the person of the woman in whom the delectable objects of all the senses are found established together? Such a combination of the delectable objects of all the senses is found only in the person of the woman and nowhere else. The woman who is good looking, young, endowed with auspicious physiognomic marks and is amiable and skilled in the fine arts, acts as the best virilific".

In the Section on virilification several preparations are described, which "impart stallion-like vigour and increase the pleasure of sexual

union, virility and progeny". Some of the descriptions sound very enticing, such as the following: "One who drinks milk after a meal of the Sastika rice mixed generously with ghee and with black gram gruel, remains awake with an undiminished sex urge through the entire night". "The man who has eaten his surfeit of the cock's flesh fried in the semen of the crocodile, cannot sleep during many nights owing to continual erection of the phallus".

"Even a septuagenarian obtains the sexual urge of youth by taking Meda milky yam etc. with milk, honey, ghee and sugar"..."He will not suffer phallic depression or ejaculation throughout the night".

Sex is a subject of abiding interest to most people. Sex is also a subject about which people feel insecure and hence gullible. Hence when Charaka states that "we shall describe preparations which invigorate the weak and which increase the virility of the strong and enhance their enjoyment", it will have a tremendous appeal, and an assured clientele. The important problem is how to establish objectively and scientifically the validity of such claims, by methods other than the subject's self-assessment (which may or may not be reliable).

Complexity of the Subject

Although sexual capacities are inborn, human beings must learn to engage in sexual acts and to experience sexual feelings in certain personally and socially acceptable ways. The spontaneous expression of the sexual instinct is greatly modified before and during marriage by social, economic, religious and cultural forces, acting in different ways in different societies. It is not correct to assume a uniform pattern of sexual behaviour common to all mankind; in fact the range and diversity of human sexuality are its most remarkable features. Charaka fully appreciated this fact, as is evident from the following quotations from *Charaka Samhita:*

"There are men that are great in size and strength but feeble of sexual capacity. Some there are, small in size and strength of body but powerful sexually. There are some who mate with women many times like sparrows, while others, though not mating many times, are given to copious seminal discharge like an elephant".

"Some men get invigorated by the season, some get steadied by constant practice, some maintain their virility by means of virilific preparations and some are virile by nature".

"The semen gets diminished by old age, anxiety, disease, strain of

labour, fasting and excessive sexual indulgence. By fear and suspicion, by grief, by seeing deformities of a woman, by lack of response in the woman, by abstention from sex, and just after full sexual enjoyment, a man is rendered incapable of mating with a woman''.

Hence if sexual behaviour and its physiology and pathology are to be discussed in a realistic way, account must be taken of the modifying forces by which sexual impulse is restrained, diverted or distorted.

Scientific Study of Sexual Behaviour

Sexual intercourse, in all its details, has never been a topic of polite conversation. Such a personal and private affair is hardly suited to the scrutiny of inquisitive scientists. In the 1940's Alfred Kinsey in USA used the questionnaire technique to gather data on sexual behaviour of the human male, later followed by a similar study on the human female. In the 1960's William Masters and Virginia Johnson gathered data on physiological and anatomical changes that accompany sexual intercourse, using techniques of direct observation, photography and laboratory measurements. During sexual intercourse there are increases in blood pressure, heart rate and respiration rate as well as other physiological changes. Increasing sexual excitement culminates in a climax or orgasm, accompanied by ejaculation of semen in the male; the changes of orgasm are more subtle in the female. With orgasm comes a relief of the tensions that have built up, and the body then gradually reverts to the normal state. While a female is capable of experiencing a second, third or even a multiple series of orgasms, at this stage, the male passes through a refractory period in which no amount of stimulation will induce a second erection. The duration of this phase varies with the individual and the occasion.

There is a wide variation in the frequency of sexual intercourse, depending on the needs and desires of the individual. In the Kinsey report, the extremes varied from one man who had ejaculated only once in thirty years, to another who claimed to have experienced thirty orgasms a week over a period of thirty years; the average number of orgasms most people experienced was three per week.

Many people have an obsession and preoccupation with sex and have unrealistic expectations from their sexual performance. Nature never meant sexual performance to be like a circus, hence a sustained overnight erection is not physiological. In fact, in medical terminology priapism or sustained erection is a pathological condition due to thrombosis of the penile veins.

Patients consult physicans more and more frequently because of disturbances in sexual function. Male sexual dysfunction may be manifested in various ways: loss of desire, inability to obtain or maintain an erection, premature ejaculation, absence of emission or inability to achieve orgasm.

Lack of arousal during intercourse, or failure to achieve orgasm, or painful intercourse (dyspareunia) are common feminine complaints.

To understand and treat sexual pathology a basic understanding of the physiology of sex is useful.

Physiology of Sex

The sex drive is controlled by an area in the brain called the limbic system and posterior hypothalamus. Its expression is influenced by cultural and psychological factors quite as much as by instinctual drives. In man, as a result of evolution, the influence of the cerebral cortex on the limbic system and hypothalamus has largely freed human sexual response from its physiological roots. Reason, learning and experience mediated by the cerebral cortex are powerful influences on human sex drive.

In human beings, as in all animals, the sex drive has three components:(1) instinctive behaviour patterns, which are genetically "programmed" into various sites in the limbic system and posterior hypothalamus, (2) sex hormones, which in part activate these patterns, and (3) an innate tendency to respond sexually to certain environmental stimuli, or releasing factors.

The hormone responsible for sexual response in both men and women is largely the male hormone testosterone (produced in the testes of the male and in the adrenal glands of both sexes). The female sex hormones, estrogen and progesterone, which determine sexual receptivity in the female of most animal species, seem not to be important factors in the sex drive in the human female, although they are essential for ovulation and pregnancy and may be important for the development of the maternal instinct.

Although the development of adult human sexual behaviour depends upon the surge of sex hormones at puberty, many components of the adult pattern appear in children and are expressed in the form of play and experiment.

Response to a sexual stimulus is a simple reflex, which depends on

the presence of sex hormones and can be modified by learning, by conscious or unconscious thoughts and by memories. If the genitals or the surrounding areas are touched, the stimulus is relayed through a reflex arc to the spinal cord and out again to the organ, the penis or clitoris, which responds by swelling. At the same time, the sexual stimulus is conducted along nerve fibres to the brain where a sexual sensation arises and is linked with past experience. Both the situation and the learned response will affect the way the individual reacts.

In many animals, especially the higher mammals, exposure to other members of the same species during infancy is crucial to the later development of sexual behaviour. Chimpanzees kept in isolation until puberty never learn to mate; studies of feral children, brought up in the wild by animals, suggest that the same may be true of humans.

Development of the Sex Impulse

The age at which sexual maturation (puberty) occurs has been given in *Charaka Samhita* as (14) for boys and (12) for girls.

As a result of improved general health and nutrition, in all societies, girls are likely to reach menarche at an age earlier than did their mothers. During adolescence there is usually a passing phase of homosexual interest, and early sexual attractions are often of this nature, most commonly among those in single-sex boarding schools. The sexual segregation of adults, in jails, army barracks for example, also promotes homosexual behaviour. The distinction between a hetero or a homosexual interest is not, however, absolute, and some individuals may be capable of enjoying sexual outlets of both types. Hence medical attitude towards homosexuality has changed, from a disease to a normal variation. Social attitudes are still in a process of crystallization, with intense opposition and total acceptance forming the two ends of the spectrum. This subject is discussed in a separate section.

After puberty, in the male, thoughts and fantasies of a sexual nature result in involuntary erection of the penis, and during sleep erection occurs from time to time as does seminal ejaculation. Erection during sleep occurs too in infants, satiated males and impotent males and in the latter excludes any organic cause of impotence. The level of sexual tension and hence the frequency of diurnal erections and nocturnal emissions varies greatly among normal individuals. Voluntary relief from feelings of sexual tension may be sought through masturbation, i.e. by conjuring up fantasies of a sexual nature and simultaneously

stimulating the sexual organs manually until orgasm results. There is no mention or discussion about masturbation in Ayurvedic literature.

Medical & Social Attitudes towards Sex

Medical and social attitudes towards sexual matters have shown wide swings like the pendulum. Two illustrative examples will be discussed; masturbation and homosexuality. It is interesting to note that there is no mention of either of the two in Ayurvedic literature. In Vatsyayana's *Kamasutra* one finds description of homosexual practices.

Masturbation: Although the Greek philosophers commended it, during the period of "Enlightenment" in Europe the medical dogma held masturbation as a cause of several evils including insanity and death. Benjamin Rush (1746-1813), a leading physician of his time and the Father of American Psychiatry held this opinion which held sway right up to the 20th Century. Henry Maudsley who was the foremost psychiatrist of his age wrote in 1867, "the sooner the masturbator sinks to his degraded rest, the better for the world which is well rid of him". Sigmund Freud wrote in 1912, "Masturbation is an infantile sexual activity which is definitely a cause of neurosis and possibly of organic injury as well".

In the mid-nineteenth century, the New Orleans Medical and Surgical Journal commented editorially: "Neither plague nor war, nor smallpox nor a crowd of similar evils have resulted more disastrously for humanity than the habit of masturbation; it is the destroying element of civilised society".

In 1858 Isaac Baker Brown, a London Surgeon introduced the operation of Clitoridectomy because he believed that masturbation in women caused hysteria, epilepsy and convulsive disorders.

Castration was performed on male masturbators (onanists) to restore their good health and useful life.

In an address delivered to the "Stomach Club" in Paris in 1879, Mark Twain said the following about masturbation, which was then considered to be an illness:—

"Homer in the second book of *The Iliad,* says with enthusiasm, "Give me masturbation or give me death". Caesar, in his commentaries, says, "To the lonely it is company; to the forsaken it is a friend; to the aged and to the impotent it is a benefactor; they that are penniless are yet rich, in that they still have this majestic diversion". In another place this experienced observer has said, "There are times

when I prefer it to sodomy". Robinson Crusoe says, "I cannot describe what I owe to this gentle art". Queen Elizabeth considered it "as the bulwark of virginity". The immortal Franklin has said, "masturbation is the mother of invention". Michael Angelo said to Pope Julius II, "Self-negation is noble, self-culture is beneficent, self-possession is manly, but to the truly grand and inspiring soul they are poor and tame compared to self-abuse".

Mark Twain was jesting. Almost a hundred years later, the modern sex therapists are in deadly earnest about the beneficial effects of masturbation. Masters and Johnson promote masturbation because they think it is therapeutic—maritally as well as medically. In the 19th Century, masturbating was an illness and not masturbating was a treatment; today not masturbating is a disease and masturbating is a treatment! It is offered as a nine-step masturbation programme by two University of Oregon Psychologists, Lobitz and Lopiccolo. The therapeutic powers of masturbation are now propounded with the same smug professional conviction with which its pathogenecity had been propounded in the past. The Sex Information and Education Council of USA has supported masturbation because it is natural.

Homosexuality

Throughout the history of mankind most cultures have promoted heterosexuality and marriage hence any deviation from this pattern was considered to be abnormal, or pathological.

The attitude towards homosexuality has also undergone a radical change. While traditional psychiatric opinion considered exclusive homosexuality as a disorder of psychosexual development, the American Psychiatric Association in 1973 decided to delete homosexuality from its official list of mental diseases. Some have gone even further to claim that homosexuals are more sexy than heterosexuals. William Simon, a senior Sociologist at the University of Indiana's Institute for Sex Research, says that he pities the man who is trapped into heterosexual monogamy. "Men who are exclusively homosexual can engage in sexual activity from many more angles, playing many more roles".

The sexual system develops as such an integral part of personality development that sexuality and personality are inseparably interwoven. The physician should not automatically conclude that every homosexual who consults him for any medical problem wants to become

heterosexual. In fact, most homosexuals prefer their sexual adaptation; and only those who are in great distress about their homosexual behaviour should be considered for psycho-therapeutic intervention. Family pressure for intervention is insufficient reason to undertake intervention.

Since 1980 over 3000 cases of AIDS (Acquired Immunodeficiency Syndrome) have occurred in USA, with almost 100 per cent mortality. The agent causing AIDS (virus) is transmitted sexually, parenterally and perinatally. Since 75 per cent of AIDS has occurred in homosexuals, they are justifiably frightened, and AIDS has started to modify their sexual behaviour.

Premarital Sex and Its Problems

Western Societies being "open societies", it has been possible for social scientists there to obtain data on this subject from large sample populations. What the position is in India is a matter of conjecture. The most well-known study of this kind is the Kinsey report, in U.S.A.

The problem of pre-marital coitus is characteristically presented by the unmarried girl who asks her physician for the contraceptive pill. Since sexual behaviour has intimate links with morality, discussion of this subject cannot be valid from a purely medical viewpoint. If freedom of the physician is not restricted by his own set of values, this provides him an opportunity to discuss with the young patient her feelings and expectations about her actual or intended partner and to consider objectively the arguments for and against such a behaviour.

It may be asserted that since due to social and economic and political pressures (e.g., postponement of marriage till age 25 by state decree), the age of marriage has to be deferred, premarital intercourse is biologically natural and that emotionally it is a helpful prelude to the marital relationship. Kinsey's data provide no evidence that premarital coitus promotes the success of the sex relationship in marriage, but indicate that there is a predictive correlation between the individual's response before and after marriage. Among women who had never experienced orgasm from any source before marriage, those who had premarital coitus fared worse in marriage than those who had not.

The modern Western teenager is in a situation where he or she is impelled to participate in activities due to group pressures and need for conformity. There may be strong pressures upon a boy to prove his masculinity or project an image of being thought as experienced and

worldly. The girl is oppressed by the fear that she will lose her boy friend if she does not agree to intercourse. The price paid by teenagers in an ever-increasing measure is considerable: unwanted pregnancy and venereal disease. Western thinkers & sociologists are concerned about sex and drug abuse in their young population but seem to be nowhere near a solution. Slowly the opinion is veering *away from permissiveness towards self-discipline.* Before long they may realise the wisdom of the ancient Indian civilization which prescribed *"Brahmacharya"* (total sexual abstinence) upto the age of 25 years, the formative period when the emphasis is on education. This is followed by *Grihasthashrama* wherein full opportunity is available for enjoyment of sexual pleasure.

Revival of the Concept of Brahmacharya

Human sexuality has moved far from its biological origins, with reproduction and perpetuation of the species as the prime motive force. Both for the individual and for society it has come to serve many purposes besides that of reproduction. The recreational (as against procreational) sexual activity serves to strengthen the male-female relationship and thus helps to ensure a stable family background for the growing child during its many years of dependence. A satisfactory sexual relationship can be maintained if man and woman share a close understanding, companionship and mutual respect. The ability to create and sustain an unselfish relationship with a member of the opposite sex is a valid measure of emotional maturity. It seems Western sex education by emphasizing merely the physiology of the sex act, is completely missing the essence of the beautiful sexual relationship. It is a tragic example of emotional immaturity and poverty of affection in the midst of material affluence.

Considering that teen-age and adult permissiveness has led Western society nowhere near happiness, time has come to pay attention to the ancient Indian concept of self-discipline in sex, especially in the formative years of adolescence.

Medical Profession & Sex Counselling

The act of sexual intercourse gives rise to two conditions that people have often found undesirable and hence sought to prevent—namely pregnancy and venereal disease. According to a survey of sexual behaviour in young people by Schofield, in 1965, among young women aged 17-19 with experience of pre-marital intercourse, one in

three is likely to become pregnant as a result. About one-fifth of the children born in Britain to women under the age of 20 years are illegitimate. The incidence of gonorrhoea in the Western countries has increased greatly in recent years. Since the prevention of conception and venereal disease requires medical knowledge, the physician must indeed be involved in sexual problems. That is why conception and prevention and treatment of venereal disease have formed two portals through which physicians entered the area of human sexuality. A third portal is formed by the disturbance of sexual function such as impotence and frigidity.

It is relatively easy to diagnose and to deal with medical causes of impotence. Several types of neurological disorders can cause impotence, including lesions in the anterior temporal lobe of the brain, spinal cord disorders, diabetic neuropathy, tabes dorsalis, and certain drugs acting on the autonomic nervous system. Such causes account for a mere 10 per cent.

Far more frequently, impotence results from psychological disturbances including anxiety and depression, disinterest in the sexual partner, fear of sexual incompetence, marital discord, worry, fatigue and general ill-health.

The present-day openness about sexuality does not necessarily mean that people are better educated on sexual matters. Many practising physicians feel that they are not competent to deal with sexual problems. Others feel that sexual counselling will be too time-consuming or will lead to an excessive involvement with emotional issues. The physician's own moral and ethical positions or personal discomfort with areas of sexuality such as homosexuality or sexual deviance, may inhibit communication. Additionally, the potentially seductive aspects of an open discussion of sexuality can be disturbing both to physician and patient.

Modern Sex Therapy

Dr. Thomas Szasz, a psychiatrist practising in New York has made a most scathing criticism of the current "sex therapy" propounded by Masters and Johnson in U.S.A.

It is interesting to note that Masters himself believes that save for himself and his colleague Johnson (who is now his wife), there are hardly any honest and competent sex therapists in America.

Dr. Szasz asserts that Masters' opinion that "the vast majority of

sex clinics offer little more than a superficial sex education at best and dangerous quackery at worst'' is equally applicable to Masters himself. In an interview to *Time* magazine in 1974, Masters acknowledged that his cures of impotent men were due largely to the efforts of the prostitutes he procured for them, under the euphemism ''Surrogate wives''. Masters regrets having had to give up the surrogate therapy due to legal hassles. As a consequence the success statistics with single impotent males in his hands have completely reversed to a failure rate of 70 to 75 per cent. For centuries, prostitutes, the oldest of the professions have been helping men to cope with sexual dysfunction.

The fraud committed by Masters and Johnson and the genre of modern sex therapists, according to Szasz, is to medicalise the problem of sexual dysfunction. Clearly, Masters and Johnson are late-comers to the game of calling prostitution 'sex therapy' and sex therapy a 'medical profession'. By encouraging surrogate wives, the modern sex therapists have ''rediscovered the wheel'', as is evident from the quotation in the beginning of this Chapter wherein Charaka described ''a young, amiable and skilled woman as the best virilific''.

Modern Surgery for Impotence

Inability to have an erection is being overcome now by means of implanting penile prostheses. These devices are of two kinds—rigid and inflatable. The first technique consists of the implantation of one or two semi-rigid silicone rods into the spongy tissues of the penis. This produces a permanent erection which the patient must conceal.

Frank Cerow, a Baylor University Plastic Surgeon stresses that the issue of how the man became impotent is not important for the surgeon, who merely serves as a technician who implants the penile prosthesis so that the patient is able to use his penis for satisfying coital function. ''It is important that women be not super-familiar with what's being done. This is a man's operation for a man's problem''.

The inflatable penile prosthesis consists of two expandable balloon-like cylinders which the surgeon inserts into the corpora cavernosa (the spongy tissue of the penis that fills with blood in normal erection). The cylinders are connected by tubing to a small reservoir buried behind the abdominal wall, and to a pump inserted into the scrotum. To make the penis erect the man squeezes the pump, forcing fluid into the cylinders and distending the penis. A release valve on the pump reverses the process.

F. Brantley Scott, a professor of urology at Baylor University College of Medicine in U.S.A. and one of the developers of this device, had by 1980, already performed over 250 implantations of his inflatable prosthesis. Doctors performing these expensive operations (rigid prosthesis $3500, inflatable prosthesis $9000) claim that "implanted men are among the happiest of the patients they have ever seen".

According to a *Time* magazine report, 10th December 1979, tens of thousands of US males ranging in age from under 19 to over 80 have already received penile implants.

Another recent operation is called penile bypass surgery. Just as the Coronary artery bypass graft surgery is intended to increase the blood supply to the heart, the penile bypass surgery is intended to increase the blood supply to the penis. Dr. Adrian Zorgniotti, Clinical Professor of Urology at New York University, asserts that vascular disease which is known to affect the heart, the brain and the kidneys is now being shown to be responsible for as many as 80 per cent of cases of organic impotence.

Female Sexuality

The discussion about virilization in Ayurveda is male-oriented and there is no mention about feminine sexual problems. It is a traditional belief that sexual arousal and response in women are inherently slower than in men. Both Kinsey and Masters & Johnson have challenged this opinion. Because she is less responsive to psychic stimuli, the woman may not become aroused until continuous physical contacts are established. For the same reason the progress of her response can be arrested by any discontinuity of physical stimulation. Given uninterrupted physical stimulation, the response of the female to the point of orgasm, whether during coitus or masturbation, can be no less rapid than that of the male.

In women, frequent sexual arousal without relief of orgasm, over the years, can result in a chronic congestion of the pelvic organs with consequent gynaecological disturbances. More and more women are consulting physicians because of disturbances in sexual function. Lack of arousal during intercourse, or failure to achieve orgasm is a usual complaint. Painful intercourse (dyspareunia) is a less frequent complaint. Vaginismus (painful spasm of the vagina during intercourse making penetration difficult or impossible) is a rare complaint.

With the widespread use of contraceptive "pill" and abolition of

the fear of unwanted pregnancy, the female is now the stronger sex—she is ever willing and ready while the male is not!

Female sexual capacity is comparable with that of the male, although women are more strongly influenced by convention and culture. While the sexual capacity in the male reaches a peak during adolescence and then gradually declines, the sexual drive of the female increases in middle age. Although sexual activity becomes less frequent as individuals become older, there is no physiological reason why it should not be continued into old age.

Sexuality & Ageing

Sexual capacity in humans can continue throughout life into old age although, with the passage of years the sexual impulse becomes less powerful and is more readily quenched by other emotions and circumstances. It seems that like many other activities, continued sexual performance depends on practice. Although celibacy carries no dire penalties, ill consequences may arise for either sex when there is frequent sexual arousal without relief of orgasm. Individuals of either sex may seek to escape from this sense of decline by engaging in sexual adventures in a forlorn attempt to recapture the experience of youth. But a satisfactory sexual relationship can be maintained between elderly couples if they share a close understanding, companionship and mutual respect. The ability to create and sustain an unselfish relationship with a member of the opposite sex is a valid measure of emotional maturity. It appears that many men grow old without attaining that maturity.

In men, testosterone production may increase as a result of regular intercourse, leading not only to increased sexual capacity but having general beneficial effects on energy and non-sexual drive.

Chapter 20

HYGIENE AND PUBLIC HEALTH

Introduction

Charaka enjoins constant vigilance and a regular, daily and seasonal routine of prophylactic measures for the maintenance of health and vigour. He also considers the influence of geographical environment, climate, water supply and seasonal variations. Vagbhata has considered preventive medicine under the *Rogananutpadaniya* measures.

The global eradication of smallpox in 1979 represents a major milestone in the history of medicine. It has demonstrated what can be achieved when governments and people throughout the world join in a common purpose of eradication of disease. This chapter is designed to illustrate and emphasize the elementary truth (alas, too often ignored or forgotten!) that prevention is better and cheaper than cure, and to show the imperative need to change the thrust and shift from curative medicine for a limited number of people to preventive medicine for all.

Story of Smallpox

Smallpox is perhaps the most infectious disease of man. At this time smallpox is considered to no longer exist in nature. In 1967 the World Health Organization launched an ambitious programme aimed at total eradication of smallpox. Two important epidemiological factors which suggested that this was possible were the absence of non-human reservoirs of the virus and the apparent non-existence of completely asymptomatic human carriers. As a result of this astonishing effort, the last recorded case of naturally acquired smallpox occurred in Somalia in 1977. After two more years of worldwide surveillance with no further infections, global eradication of smallpox was confirmed in 1979 and accepted by WHO in May, 1980. This was followed by destruction of laboratory stocks of the virus with the exception of six laboratories in various parts of the world. Surveillance continues, including studies of

pox viruses of animals which are antigenically somewhat similar to smallpox. Some virologists remain legitimately concerned that an animal pox virus (like monkey pox, white pox) could undergo mutation and become virulent for humans, although the chance of such an occurrence seems remote. Also, the possibility of "escape" of virus from a laboratory, although unlikely, must be considered.

Because the disease appears to be eradicated the story of smallpox may be now more of historical than practical interest. Even then a historical review of smallpox has great educational interest. From ancient times smallpox was a major cause of mortality. Those who survived were left blind or scarred. In the 17th Century smallpox was endemic everywhere in Europe and probably throughout the world. It was even more fearful and loathsome than plague. Scarcely 20 per cent of the population escaped it entirely, and it was always more virulent in the cities than the country side, more in the poor than in the rich. By experience, common folk learned that smallpox could not be cured but it could be prevented. People in many parts of the world had practised one method or another of "buying the pox" long before Jenner's time. Fearful for their children's health, parents would seek out some one with an infection of smallpox, preferably a mild one. The smallpox victim and the child would then make contact in such a way as to infect the child. After an incubation period of about a week the child, if he was lucky, would develop a mild case of smallpox and would emerge virtually unscarred and immune to the disease thereafter; the mild induced infection gave the same protection that was provided by a severe one. Educated people came to call this practice of folk medicine *inoculation* after the Latin *inoculare,* to graft. They also called it *variolation;* variola, from the Latin *varus,* pimple, was the scholarly name for smallpox.

The Chinese avoided direct contact with the sick; instead the child was induced to inhale a powder made from the crusts shed by a recovering patient. In the Near East and Africa, fresh material from a diseased patient's pustules was rubbed into a cut or scratch in the skin of the person being immunised. Professional variolators, usually women, took material from a ripe pustule and rubbed it into a scratch in the arm or leg of the person being inoculated.

In 1715, Lady Mary Wortley Montague, a beautiful English woman developed smallpox which ruined her beauty. The following year her husband was sent as ambassador to the Turkish Court in Constantinople. Lady Mary, who now had an understandable interest in smallpox, was greatly impressed by what she saw of the Turkish practice of

variolation. She got her own son inoculated and after her return to London in 1718, she agitated enthusiastically in favour of variolation and got her four-year old daughter also inoculated.

In 1778, Catherine the Great in Russia summoned a London physician Thomas Dimsdale to St. Petersburg to inoculate her and her son and heir, the Grand Duke Paul. On doing the act without mishap, Dimsdale received from the grateful Queen a cash gift of 10,000 pounds and another 2000 pounds to cover expenses; and she also established an annuity of 500 pounds for him. This must surely be the highest compensation paid by any one in exchange for immunity against smallpox.

Everywhere in Europe a majority of the well-to-do had been variolated in the 18th Century. As for the urban poor, they seemed to have shown no great interest in the issue.

Edward Jenner (1749-1823), a physician in country practice, noted in 1790's that the dairymaids in his neighbourhood rarely, if ever, contracted smallpox even in the absence of variolation. The cowpox and human smallpox viruses probably stem from a common ancestor and are closely enough related to produce a cross-immunity, but as diseases, behave quite differently. Cowpox occurs as a few small skin ulcers in cattle and human beings, whereas smallpox is a serious, spreading, and often fatal ulceration in man and some monkeys. Folklore wisdom knew about this cross-immunity long before the medical profession did.

In 1796 Jenner inoculated material from a dairymaid's cowpox lesion into the arm of an eight-year old boy, who was subsequently immune to the effect of smallpox variolation. Jenner called the new procedure vaccination (*vacca* for cow). After two years of careful observation and experiment he published in 1798 a 70-page pamphlet—"An inquiry into the causes & effects of the variolae vaccinae". Variolae vaccinae was *cowpox,* the bovine form of smallpox. In this classic report Jenner advanced the notion that inoculation with cowpox, which he considered a mild form of smallpox, would provide the same immunity to smallpox that variolation did. What was more important, the disease produced by vaccination as opposed to variolation, would be so extremely mild that the vaccinated individual would not be a source of infection. Jenner predicted that "the annihilation of smallpox must be the final result of this practice".

Jenner's thesis was accepted at once by the great majority of physicians, and within a year or two thousands had been vaccinated. Jenner was hailed everywhere as mankind's greatest benefactor, and his

discovery was characterised as the most important medical advance of all time. In 1802 Jenner received recognition by a Government gift of £10,000 and a further £20,000 five years later.

In 1796, one-fifth of all deaths in London were ascribed to smallpox. Vaccination was introduced in 1798 and made compulsory in 1852. Owing to the decline of smallpox, in 1971 it was decided in U.K. that vaccination should no longer be routinely recommended.

Since there is no known animal or insect reservoir of the virus of smallpox, for infection to persist in a population one afflicted person must transmit the virus to a susceptible contact, and that contact must transmit it to another in an unbroken chain. The smallpox victim can transmit the disease only from the time his rash appears until the scabs drop off, a period of about four weeks. After that he is immune to reinfection. Increasing population densities provide enough susceptible individuals to sustain the chain of transmission. In isolated villages and among scattered populations a point is reached where so few people remain susceptible that the chain of transmission is broken. It seems reasonable to speculate that in ancient times only the more densely populated areas of India and China were able to sustain the continued transmission of smallpox.

When WHO was established in 1948 as a specialized agency of the United Nations, it approached the smallpox problem gingerly at first. The Pan American Sanitary Bureau (now the WHO Regional Office for the Americas) demonstrated how smallpox could be eradicated from North America. By 1959 smallpox had been effectively eliminated from all American countries except Argentina, Brazil, Columbia, Ecuador and Bolivia. In that year, on the initiative of the USSR, the World Health Assembly called for global smallpox eradication and vaccination in foci where the disease exists. The WHO and UNICEF helped a number of countries to establish vaccine production centres. Potent dried vaccine was an essential tool that could make the eradication of smallpox possible. Progress was however, slow. Lack of skilled personnel, vehicles and other necessary assistance, poor quality of vaccines, all contributed to tardy performance.

In 1966 delegates to the World Health Assembly voted a special budget of $2.5 million for an intensive programme to begin on January 1, 1967 with an objective to eliminate smallpox from the globe by the end of 1976.

The bifurcated needle, developed at Wyeth Laboratories in the 1960's simplified the vaccination procedure, requiring only a quarter as

much vaccine as for the scratch technique. In Africa, a new strategy of surveillance-containment was developed: improved search and detection of cases as speedily as possible, isolation of patients and vaccination of every known or suspected contact around them. The procedure sealed off outbreaks from the rest of the population. This technique was introduced in India in 1972.

In October 1973, the smallpox eradication programme in India conducted the first of a series of week-long searches that were scheduled once a month and involved more than 100,000 health workers. The first one-week search yielded more than 7,000 cases in a population of 90 million. Rewards were offered for reporting smallpox cases. As reporting improved, more than 2,18,000 cases were reported in India in 1974, the highest total recorded since 1958. By careful case detection, containment and mass vaccination of contacts, eventually smallpox was eradicated from India in 1976. No fresh case has been reported since, although a reward of Rs. 5,000 is offered officially for any new case reported.

Importance of Pure Water & Sanitation

The importance of pure drinking water and air, and the relationship of filth and over-crowding with disease was known to ancient civilizations. The excavations of Mohenjodaro and Harappa (circa 2500 BC) indicate well-planned cities with a system of aqueducts for supply of water and a system of latrines and drainage. In *Ramayana,* the ancient Hindu epic, at one place Laxmana alludes to a particular sin being *"even greater than the polluting of drinking water".* The Romans realised the connection of marshes surrounding Rome as fertile breeding grounds of mosquitoes, with malaria, and from the 7th Century BC they drained the marshes. By the 6th Century BC Rome was furnished with a network of underground sewers including its main drain, the Cloaca Maxima. The Tiber was replaced as a source of water supply by aqueducts bringing pure drinking water from miles away. By the 2nd Century A D fourteen such aqueducts supplied Rome with an estimated 40 million gallons of drinking water a day. The poor carried it from public fountains, the affluent had it piped into their homes. Unfortunately the ancient Indian and Roman tradition of hygiene and public health was lost in the subsequent centuries and contamination of drinking water brought untold misery and devastation right upto the 20th Century.

The Story of Cholera

Cholera is one of the most perplexing of all epidemic diseases. The

name derives from the Greek *Chole* for bile and biliousness, and *rein* to flow—the loose rice-water diarrhoea. In Ayurveda the word used for it is *"Visuchica"*. In Hippocratic writings one finds a description which tallies with cholera although the word is not used as such. "Herophrotus was ablaze with an acute fever; his stool was watery and bile-coloured; even a slight touch caused great pain in his abdominal muscles; on the fifth day of his fever he began to ooze sweat; eventually he collapsed".

The description could also apply to typhoid or dysentery. Some ancient clinical descriptions are so ambivalent that they could be applied to any one of several diseases as we know them today.

A Greek notation of a frightful epidemic was inscribed on a monolith by some soldier or officer in the invading army of Alexander the Great (356 – 323 BC) penetrating India. The inscription states: "The lips blue, the face haggard, the eyes hollow, the stomach sunk in, the limbs contracted, those are the signs of the great illness which, invoked by the malediction of the priests, comes down to slay the brave".

The Ganga river delta in India is probably the earliest home of cholera. In recent years the Celebes Sea Islands have been identified as a focus of the El Tor strain (name of the quarantine station on the Red Sea where this particular vibrio was first isolated in 1905 in pilgrims returning from Mecca).

Without warning, cholera has swept out from its traditional home, often in pandemics, killing uncountable millions in Asia, Africa, the Middle East and on occasion parts of Europe and the Western Hemisphere. Just as swiftly, without warning, it has retreated, leaving behind little to explain why it came, and little to say when it will come forth again.

The Chinese today use "hua luan" as the term for cholera but in their ancient literature the term covered a mixed bag—gastroenteritis, colic, appendicitis, besides cholera. Arabic medical writers had no word for cholera.

Religious pilgrimages and military operations were responsible for the spread of cholera from its home in India. A historian Gasper Correa (Circa 1560) visiting Malabar Coast of India under Portuguese control, noted several striking epidemics of cholera. In the spring of 1503 there was a high death rate in the army of the sovereign of Calicut. Correa noted "a sudden-like disease which struck with pain in the belly and

diarrhoea, so that the man did not last out eight hours' time''.

A pandemic that broke out in Bengal in 1817 attacked every one, all castes, all ages and all nationalities. A British Army group under the Marquis of Hastings lost more men simply marching through Bengal than it probably would have lost in a major fighting engagement. In a diary entry made on November 17, 1817, the Governor General of India wrote ''Above 500 men have died since sunset yesterday''.

The infection spread to Ceylon, Java, Borneo and other Indonesian islands between 1819 and 1830. Java alone lost 100,000 lives. Sailors brought it to Japan from Java. In Nagasaki and Osaka it took a terrible toll in human lives. In 1819 the island of Mauritius experienced an epidemic of cholera that killed 6000, mostly Negro slaves. The second leap brought it to Africa in 1820 and 1821, killing hundreds of thousands. In 1821 cholera appeared in Basra, then the main port at the head of the Persian gulf. Three weeks later, 18,000 were dead. From there the infection moved to Baghdad, carried by boats on the Tigris river and the camel-backs in caravans. It killed thousands of soldiers of the Persian army then besieging Baghdad.

The second pandemic came out of India on caravans in 1828 and 1829 to Afghanistan and Persia. From there the caravans carried cholera further to European Russia. It flowed into Europe through Orenburg on the Ural river and from there to the Americas on the immigrant flow in a matter of a few months.

''Vomiting death'' reached Moscow in 1830. From there it flooded the Baltic States and moved further west in Europe. Belgium alone lost 8000 people in 1832. By the end of that year some 14790 Englishmen had been struck down in an epidemic fanning out from Sunderland, of whom 5432 died.

In 1849 New York City was figuratively a funnel through which cholera poured into the United States. In the same year, a significant discovery was made by Felix Pouchet (1800 – 1872) in France, when he reported finding *vibrios in the stools* of cholera patients. At the time however, Pouchet's discovery made little impact of value to public health.

John Snow, a London anaesthesiologist studied the epidemics of cholera in the 1840's and became convinced that *polluted water* was responsible for the cholera epidemics. An epidemic of cholera occurred in London in the summer of 1853, which gave Snow a chance to test his hypothesis about the spread of cholera. The Lambeth Water Company,

which had moved their works upstream to Thames Ditton, obtained relatively pure water from the Thames. The parts of London supplied by this company were also supplied by the Southwork and Vauxhall Company which drew their water from the Thames river at Battersea, a very polluted part. Snow found out that in the district supplied only by the Southwork and Vauxhall Company the death rate from cholera was 114 per 100,000 population, while it was 60 per 100,000 in districts supplied by both companies, but there was *no death at all* in districts supplied exclusively by the Lambeth Company. These results were very suggestive to Snow, but by no means conclusive.

The next year Snow sought better evidence. When an epidemic occurred in July, 1854, he obtained the address of every one who died of cholera in districts where both water companies were operating, and personally visited their houses to ascertain which supply was taken by whom. His calculations showed that the rate of cholera deaths per 10,000 houses was 14 times more among those supplied by the Southwork & Vauxhall Company than among those supplied by the Lambeth Company. Within a radius of 250 yards of a particular water pump at the junction of Broad and Cambridge streets, 500 people suddenly died of cholera within 10 days. Snow personally saw to it that the handle of the Broad Street pump was removed. The epidemic stopped that very day.

In a mile-stone publication called "On the Mode of Communication of Cholera", John Snow described how cholera is spread via water supply and sewage systems. Snow was the first to understand and prove cholera as a *water-borne disease.* His description is as valid today as it was when first written in 1849. "When the water of a river becomes infected with the cholera evacuations emptied from on board ship, or passing down drains or sewers, the communication of the disease is much more widely extended. I know of no instance in which it has been generally spread through a town or neighbourhood, among all classes of people and community, in which the drinking water has not been the medium of its diffusion. Each epidemic of cholera in London has borne a strict relation to the nature of the water supply of its different districts, being modified only by poverty and the crowding and want of cleanliness which always attend it".

Unfortunately lessons of public health are not quickly learnt. The third pandemic of cholera starting in 1852 and ending in 1859, was followed by a fourth and even larger pandemic again originating from India, in 1863. Its brutal tolls were even larger than before. More than

90,000 Muslim pilgrims died in Mecca in 1865. There were 90,000 deaths in Russia in 1866. Sardinia lost 130,000 lives in 1867. Zanzibar lost 70,000 lives in 1869. In U.S.A. the year 1866 ended with 50,000 dead, New York alone listing 2000 fatalities for the summer of 1866. The country was building a network of railroads west, and cholera quickly followed the trunk lines. In 1875, Hungary buried some 190,000 cholera victims.

In 1883, Robert Koch, while studying cholera outbreaks in India, cultured from the stools of cholera victims the comma-shaped germs now known as *vibrio cholera.* Their appearance by the millions in the stools of infected persons, their ability to cause fatal infection in guinea pigs on experimental infection, left no doubt about the cause-and-effect relationship of the vibrio to the disease. What Pouchet had started 40 years earlier, Koch completed. However, the discovery was of little solace to Russia where in 1893 – 1894, in the Volniya-Podolsk area, cholera claimed 800,000 deaths.

India continued to suffer enormous loss of life due to cholera— 682,649 in 1906, 579,814 in 1908, 556,537 in 1918 and 565,166 in 1919.

In December 1967, WHO stated — "Four of mankind's worst communicable diseases are on the increase, one of them being cholera. Total reported world case load is 70,000 per year, of which over 21,000 have been dying. To those may be added the thousands of unreported cases".

The vibrio of cholera attacks a single layer of cells in the intestinal tract. The exotoxin of the vibrio quickly enters the cells and causes an invisible biochemical lesion and raises the level of cyclic AMP in the cells. The result is a shift in the balance between the absorption and secretion of water and electrolytes by that cell layer. Normally each hour the intestinal wall passes four or five litres of water; ordinarily the balance inward and outward is elegantly struck. A loss of 30 quarts of water in a day in cholera is not uncommon. Death occurs, not from the Cholera exotoxin which never enters the blood stream, but from loss of fluid and electrolytes.

If prompt fluid and electrolyte replacement is made, physiological recovery of the cholera patient is remarkably rapid, and mortality exceptionally rare. The important causes of death, in inadequately treated patients, are hypovolemic shock, metabolic acidosis and renal failure resulting from acute tubular necrosis.

Since the limiting factor in treatment of cholera in both epidemic and endemic situations is often the lack of adequate quantities of intravenous fluids, the recent availability of an *oral treatment regimen* has greatly reduced the mortality from cholera outbreaks during the most recent pandemic spread of this disease. A major discovery came in 1968 that the cholera enterotoxin does not alter *glucose-facilitated sodium absorption,* hence fluid repletion can be effected by the oral administration of a solution containing 20 g. glucose per litre, or sucrose 40 g. per litre, sodium bicarbonate 2.5 g. per litre, sodium chloride 3.5 g. per litre and potassium chloride 1.5 g. per litre. This solution can be readily prepared in any village, and is satisfactory for treatment of all age groups, if started early. In 1978, the *Lancet* wrote: "The discovery that the sodium transport and glucose transport are coupled in the small intestine so that glucose accelerates absorption of salt and water, was potentially the most important medical advance of the century".

It is a matter of lasting shame for all of us that the land of *Ramayana* which considers "polluting of drinking water as the greatest sin", continues to have the dubious distinction along with Bangla Desh of hosting permanently the cholera vibrio, which is so fragile an organism that outside the human intestine it cannot survive for even a few minutes. The knowledge is all there to control cholera—human waste disposal, water purification, fly control, sanitary methods of food handling—yet we do not have the wisdom and the will to implement it.

The Story of Plague

Since ancient times plague has been a most dreaded fatal disease of mankind. It has been the subject of dread as well as source of literary stimulation to authors from Dionysius in the 3rd Century A.D. to Camus in the present. The term "black death" was first used in the 14th Century to describe the appearance of the body after death, when haemorrhages beneath the skin gave the corpse a dark mottled hue. Only in 1905 was it discovered that plague is primarily a disease of rodents, particularly the black rat, and human epidemics arise from contact with infected rats, usually through their fleas, in which the plague bacillus grows.

The origin of plague has been located to Lake Issyk-Koul in Central Asia. A natural disaster, possibly a flood, drove a host of rodents from their lake-side home. With them travelled the fleas infected with plague bacilli. As the rodents died, the fleas first found human hosts in

China where records report 13 million deaths. The first authentic pandemic was recorded in the 6th Century A.D. Travelling along the trade routes from China, with the black rats providing porterage, the plague bacillus reached India in 1325 A.D. Moving westwards it passed into Asia Minor and thence to Egypt and North Africa. Ships took rats and plague to all parts of Europe and England. As a precautionary measure against plague, ports like Genoa and Venice introduced the earliest form of quarantine (isolation of suspected cases). Christ had spent forty days (quaranta) and nights in the wilderness. Therefore Eastern traders were isolated upon a nearby island for a similar period before being admitted to the city.

The last major pandemic originated in China in 1894, spread eventually to all continents and was first recognised in U.S.A. in 1900. The disease is well established in wild rodents in many parts of the world and is present on every continent except Australia.

Major outbreaks of human disease have usually resulted from association with domestic rats, and these have usually occurred in urban areas in the wake of rat epizootics. When the concentration of people and of rats under conditions of poor sanitation provide opportunities for the migration of fleas from rats to humans, an outbreak is likely to occur. Because sylvatic plague (plague in wild rodents) appears virtually impossible to eradicate, it will continue to pose a constant threat of extension into urban rat populations and thence to humans. Because rat fleas will attack humans if rats are not immediately available, the infection is likely to be transmitted as the rat population decreases and the fleas transfer from dead hosts to human beings. Plague can be acquired by direct contact with the tissues of an infected animal, by its bite, or by scratching of infected material into the skin.

Important work on the development of a vaccine against plague was done by Vladimer Haffkine in Bombay in the 1880's.

Fortunately, for the last 50 years there have been no cases of plague in India. The availability of effective antibiotic therapy has improved the prognosis of this formerly highly fatal disease. In the past the mortality rate of bubonic plague varied from 50 – 90% and the pneumonic, septicemic and meningitic forms were almost invariably fatal. In treated cases now the mortality is 5 – 10% and even the gravest infections respond to modern chemotherapy (streptomycin, tetracycline, kanamycin, chloramphenicol), if treated early enough.

Tuberculosis

Tuberculosis ranks high as the single communicable disease causi..g the

largest morbidity and mortality in India. This disease is known to mankind from time immemorial. In the Rigveda (circa 2000 B.C.) a hymn is consecrated to the cure of *"Yakshma"*, which is very much indicative of consumption or tuberculosis. Charaka and Sushruta refer to it as *"Raja Yakshma"* probably with the connotation of consumption of the kings, as well as the king of all evils. According to Ayurveda the disease is difficult to cure. Tuberculosis is described in ancient Chinese literature as *"Laoping"*. Evidence of tuberculosis of the bones is obtained from Egyptian mummies (circa 3400 B.C.). The reference to tuberculosis appears in the Hammurabic Code, written earlier than 2000 B.C. Hippocrates described the disease and observed that attention to tuberculosis patients was a waste of time and a burden on the state. Half a century later, Aristotle expressed pity on the unfortunate consumptives. Celsus, in whose time Jesus Christ was born and crucified, described early treatment of tuberculosis for which he recommended sea voyage. In the famous Leipzig library there is a folio which contains information that Christ himself suffered from tuberculosis. In the Bible, the Israelites were warned that "the Lord shall smite them with a consumption and with a fear and with an inflammation".

In the middle ages, Arabian physicians Rhazes (850 – 923) and Avicenna (980 – 1037) wrote of the virtue of dry air and fresh asses' milk for the treatment of tuberculosis. But nothing effective was really available in the form of therapy in medieval times. In the 11th and 12th century England, the practice of touching the king's feet for the cure of the "king's evil" as tuberculosis was then called (reminiscent of *"Raja Yakshma"* in Ayurveda), was widespread. Queen Anne was the last of the English rulers who practised this quack remedy.

The infectious nature of tuberculosis was described by the Italian physician Girolamo Fracastro of Verona (1483 – 1553). The era of morbid anatomy and clinico-pathological correlation had begun in Europe and Franciscus Sylvius of Leyden (1614 – 1672) first employed the term *tubercle* to describe the lesions seen by the naked eye in this disease.

Richard Morton (1637 – 1698) described signs and symptoms of this disease in his book "Pthisiologia".

Morgagni (1682 – 1771) dissected the bodies of consumptives and was the first to describe the pathological condition of the lungs in this disease. Benjamin Morton in 1720 postulated the existence of the "germ" of tuberculosis 120 years before its actual discovery.

Gaspard Laurent Bayel (1774 – 1816) introduced the term "tuberculosis" for the first time and traced the relationship between pulmonary tuberculosis and tuberculosis of the other organs.

The art of percussion of the chest was described by Auenbrugger in 1761, and that of auscultation by Laennec who introduced the stethoscope into the practice of medicine in the early nineteenth century. The theory of contagion — of something transferred from the sick person to the healthy person causing the disease in the latter, was proposed by Jacob Henle, teacher of Robert Koch, in 1840.

Villemin (1827 – 1892) demonstrated in 1865 that tuberculosis could be transmitted to experimental animals, implying thereby the presence of a transmissible agent.

Robert Koch (1843 – 1910) announced the discovery of the tubercle bacillus on 24th March, 1882. Equally important for the science of Medicine, Koch gave the ground rules to establish the cause-effect relationship of pathogenic agents and the disease they produced. Modern science demands rigorous proofs for its hypotheses and Koch's postulates are an excellent example of validation of the scientific theories, which is most satisfying intellectually. The importance of the *"seed"* was immediately recognized, but the importance of the *"soil"* (the host factors) and the *environment* in which the seed and soil interacted, was gradually revealed in the 20th Century when the science of immunology blossomed.

The diagnosis of pulmonary tuberculosis was greatly facilitated by the discovery of X-rays by Roentgen in 1895, and its clinical use in 1904. But in the absence of effective therapy a wide variety of treatments were in vogue, with a stress on change of climate and change of environment.

A hundred years after Robert Koch's discovery of the tubercle bacillus, tuberculosis is still a major unsolved problem of world-wide dimensions. Today at least 15,000,000 people suffer from infectious tuberculosis the world over, and 3,000,000 die of it every year, according to conservative WHO estimates. In India alone there are 3,000,000 infectees every year.

Technically advanced countries have achieved spectacular results in the control of tuberculosis over the past decades. It is important to recognize the *socio-economic and environmental factors* that contributed to the control of tuberculosis in affluent countries. Fifty years prior to the discovery of the tubercle bacillus, the death rate in England from

tuberculosis had already fallen from 4000 per million to 2000, and it had already declined to 400 per million before modern chemotherapy for tuberculosis was introduced in the 1950's. Tuberculosis is a disease of poverty and overcrowding. Mortality rates from tuberculosis fell throughout the periods when personal incomes and living standards rose, and people were better housed and better fed. Specific therapy played no part in this fall, nor did specific preventive procedures. Hence in the ultimate analysis all efforts directed at the rapid improvement of the general socio-economic situation (more production in agriculture and industry, more jobs, better nutrition, better housing, limiting the size of the family to two issues only) will be contributing factors not only in the control of tuberculosis but many other health problems.

But socio-economic improvement takes time. What do we offer to the poor victims of tuberculosis in the meantime? For a disease considered till the 20th century as "so fatal as often, to deter the practitioner even from attempting a cure", modern chemotherapy has provided a silent revolution. The Tuberculosis Research Centre (TRC) in Madras, one of the permanent research institutions of the Indian Council of Medical Research (ICMR), in collaboration with the British Medical Research Council and WHO, did pioneering work in the 1950's in the domiciliary treatment of pulmonary tuberculosis and showed very clearly that patients of pulmonary tuberculosis, even continuing to live at home under very poor socio-economic and housing conditions, even continuing on poor nourishment, can be *cured by modern chemotherapy* provided it is given in combination of two or more drugs regularly for a sufficiently long time. If 100% success is not achieved today in treating tuberculosis, it is not due to failure of science but due to human failure—*default* in taking the drug regularly. The ICMR has given priority to tuberculosis and its efforts are being addressed primarily to identify more effective chemotherapeutic regimens which could bring about a cure in the shortest possible time. The TRC is at present investigating 10 short-course regimens on a domiciliary basis. These regimens are of six months' duration (as compared to the earlier 18 months) and all have shown high efficiency in preliminary trials. The need of the day is to operationalise the short course regimens which have been tested and found effective. Effective participation of the community is crucial for the success of an integrated programme of tuberculosis control, through the primary health care delivery system. It is important to realise that *supervision*

of therapy at home is the crucial component of the programme and the community has to understand its role in supervision of those who are diagnosed, and finding out new cases at an early stage where they can be cured hundred per cent. The scientific knowledge is all there today to control tuberculosis; do we have the will to act?

Leprosy

Ancient India, China and Japan recognised leprosy. The Chinese described it as "Dragon Maggot disease". Ayurveda described various stages of *"Kushtha"* and its complications and considered it incurable. Today, happily our assessment of the disease is entirely optimistic.

There are probably 10 to 20 million persons affected with leprosy in the world today. The disease is more common in tropical climates, in many of which 1 to 2 per cent or more of the population is affected. It is also common in certain regions with cooler climates such as Korea, China and Central Mexico. But in ancient and medieval times it was also wide-spread in Europe, and a fatalistic acceptance of the leprosy sufferers' lot was common. The Biblical disgust towards leprosy and the conviction that victims were either tested or punished by God, influenced the public attitude towards leprosy patients. In 583 A.D. the Council of Lyon, a weighty gathering of Clergy decreed "that lepers must henceforth associate only with other sufferers". Those who disobeyed were executed. Men bearing grudges drove their enemies into exile simply by accusing them of having leprosy (whereas in fact the skin lesions could be anything from acne, scabies or psoriasis). Society demanded that lepers don identifiable clothes whereby all could know, shame and shun them. A savage code of behaviour was prescribed for the sufferers. Leprosaria or lazarettos were opened in France, England, Italy and elsewhere in Europe. For centuries, Christians were constantly warned of the unholiness of seeking any but divine cure. "To consult physicians, to take medicine befits not religion and is contrary to purity", said the French ecclesiastic St. Bernard of Clairvaux (1091 – 1153).

In 1200 A.D. there were some 19,000 leprosaria in Christendom. By 1400 A.D. France and Germany had 10,000 between them.

There were few comforts in the leprosarium; isolation was its only purpose, neglect its only medicine, death generally its only exit. At least the inamtes were spared the abuses and cruelty of the outside world. Not every one was so cruel, however. In the 13th century the

Hungarian Princess Elizabeth left a cosy comfortable court life to feed and bathe leprosy sufferers, and died doing it at the age of 24. Today she is remembered as St. Elizabeth, patron saint of those with leprosy.

Leprosy attained pandemic velocity in the 13th and 14th Centuries. It peaked in the 15th Century, then it declined and quit. Probably the epidemics of plague that ravaged Europe for 200 years from the mid-14th to mid-16th centuries, which killed 25 million or a quarter of Europe's population, wiped out the leprosy population as well.

The leprosy bacillus was first seen and recognized as such by Hansen in Bergen in 1873. In his time the general impression was that leprosy was hereditary. Some thought it was due to a "miasma" or an infectious element which arose from the soil. Hansen's approach was methodical and stepwise. First, he studied the disease from a clinical point of view. From his anatomical and clinical investigations he drew the conclusion that leprosy was a *specific* disease, that is a distinct, well defined disease, and therefore probably with a definite cause.

Hansen's next step was epidemiological. In 1871 and 1872 he travelled around in the districts of Western Norway where leprosy was most prevalent and carefully investigated 69 families wherein some of the members suffered from leprosy. By strict application of logic Hansen found that heredity could not account for the observations made, whereas they strongly indicated an infectious origin of the disease. Through studies of leprosy patients who lived on isolated farms and in whose families no other cases occurred, he learned that these patients had always previously been in contact with leprosy cases. He further described two cases of newcomers to leprous districts from non-leprous areas, who contracted the disease. He found that both had been in contact with leprosy patients before they became ill.

Hansen then began the work of searching for the causative germ. On 28th February, 1873 he examined a boy with many leprous nodules on the face. He removed one nodule from the nostril, cut through it, carefully scraped the edge of the cut with a knife, rubbed the stuff on to a glass slide, added distilled water to lyse the cells, and observed large numbers of rods escape from the cells. These were the leprosy bacilli.

Unlike other micro-organisms which could be cultured in the laboratory and passed on to experimental animals wherein they produced fresh lesions, leprosy bacilli could not be grown in culture plates

and man is the only natural host for the germ. Lack of an animal model of the disease was a great handicap in learning about the bacillus and its response to various modes of treatment. Shepard in 1960 originally demonstrated local growth of mycobacterium leprae in the foot pad of the mouse. The growth is limited with the number of bacilli reaching a plateau of about a million bacilli per foot pad. In the logarithmic phase of the multiplication the generation time of M. leprae is 12—13 days, extremely slow when compared to other micro-organisms; this slow generation time is consistent with the long incubation time and chronicity of leprosy in man. The bacilli infiltrate nerve tissue in the foot pad, and they have characteristic morphological features as in the human disease.

The mouse model has been used much for the study of antileprosy drugs and for the study of drug resistance, a major problem in current treatment of leprosy.

The nine-banded armadillos have a lower body temperature, and a heavy systemic infection is produced in a proportion of the animals into which the leprae bacilli are experimentally injected. The bacilli multiply very slowly so that armadillo experiments take several years (mouse experiments take 6—12 months) but the higher bacterial yield from armadillos is making many immunological studies possible. Although leprosy is an infectious disease, it may to a great extent also be considered as an *immunological disease*. The germ itself is virtually non-toxic and may occur in great numbers in the skin with almost no clinical symptoms. Most symptoms of the disease are in fact due to the immune reactions against the bacilli. Nerve damage which is responsible for the dreaded deformities associated with the disease, is directly due to the cell-mediated immune reactions. Further, the extent of multiplication in the human body is determined by the host response and not by the variation in the virulence or pathogenicity of the parasite. Variations in the host response are profound and responsible for most of the variations in the clinical course after infection.

A profound lack of cellular immunity for M. leprae in lepromatous leprosy is indicated by the histology and by the negative lepromin reaction. The lymphocytes from lepromatous leprosy patients fail to react *in vitro* to M. leprae antigens. Under the same *in vitro* conditions the lymphocytes of tuberculoid leprosy patients react positively. In addition to this depressed specific cellular immunity for M. leprae, untreated lepromatous patients frequently have a partial depression of cellular immunity in general. Mice that have been rendered T-cell deficient by thymectomy and irradiation followed by bone marrow

replacement respond to inoculations of M.leprae by developing heavier infections.

In the 1950's dapsone (4-4 diamino diphenyl sulphone, DDS) provided the definitive treatment of leprosy. In a few months in lepromatous disease enough bacilli are killed to render mouse inoculations negative and to reduce infectiousness more than 99 per cent. However, in this form of the disease nonviable bacilli disappear slowly and may be found in the tissues for 5 to 10 years. Moreover, a few viable bacilli (persisters) may persist in the tissues for many years and may cause a relapse if treatment is discontinued. Consequently in lepromatous disease, treatment should be continued at least 6—10 years after bacilli are no longer demonstrable in skin smears, or perhaps for life. Sulphone resistance occurs in some patients. After 5 to 20 or more years, during which the response is favourable, such a patient will develop clinical and bacteriological relapse in spite of regular therapy, and sulphone resistance can be proved on isolates in mice. The frequency of this secondary resistance has been 2 to 30 per cent in different countries, depending on the sulphone used and regularity of administration. Occasionally, primary resistance in previously untreated patients has been described.

Because of the problem of drug-resistant bacilli and of persister bacilli, *multiple-drug therapy* is now recommended for lepromatous disease. The additional drugs most commonly used are clofazimine and rifampicin.

Many of the deformities and disabilities of leprosy are preventable through proper attention from the beginning of treatment. Plantar ulcers, which are very common, may be prevented by rigid-soled footwear or walking plaster casts; contractures of the hands can be prevented by physical therapy and application of casts. Plastic and reconstruction surgery is sometimes helpful. Nerve and tendon transplants and release of contractures can give patients more functional ability. Vocational retraining is often necessary for those with permanent disability. Plastic repair of facial deformities assists acceptance of patients in society. The psychological trauma which results from prolonged segregation is now minimized by permitting patients to continue therapy at home as soon as possible.

Based on the 1981 census population of 683.9 millions, the estimated number of leprosy patients in our country is 4 millions, which is by far the largest leprosy population in any single country in

the world. Approximately 20% of the patients will develop deformities which are entirely preventable. About 400 million people live in hyperendemic and moderately endemic areas where active transmission is continuing and are therefore exposed to the risk of infection. 72 districts in the country have been identified as hyperendemic for leprosy with prevalence rates above 5 per 1000. Tamilnadu has 19 per 1000, Andhra 14.5 per 1000. The magnitude of the problem is vast and consequently the need to achieve control gains greater urgency. Over the years, Indian scientists have been intensively working on the problems of leprosy, particularly the ICMR's Central JALMA Institute at Agra.

Case finding and chemotherapy form the present basis of control because infectiousness is quickly suppressed as is the development of deformity. Unfortunately civilization and technology have not been able to eliminate *leprophobia.* As the disease persists, so does the irrational fear and ignorant loathing about it. People need truth dinned into their ears many times and from all sides. The first rumour makes them prick their ears, the second registers and the third enters. People must be educated to appreciate the fact that though a communicable disease, *leprosy is not easily communicable.* It is less contagious than most communicable diseases. The bacillus is very slothful in its growth. Doctors and nurses who have been in contact with leprosy patients for years have never developed the disease, unlike tuberculosis which is an occupational hazard for doctors and nurses. Those who contract leprosy can now be cured. Leprosy is only a disease, not a disgrace. How long will these truths take to enter people's minds?

Hookworm Disease

Worms of various kinds have inhabited the human body throughout the nearly one million years of human existence. Worms parasitic on man fall into three important groups: round worms, tape worms and flukes. These in their adult form, range in length from a few hundreths of an inch to 30 feet in the case of the fish tape worms. The best known disease producers are the round worm, hookworm, whip worm, pin worm, schistosoma and filaria. The vast majority of worms infesting man inhabit the intestine, the most common being *Ascaris,* the large round worm (6 to 14 inches long). The second most common and probably the most troublesome of all is the hookworm (4/10 to 5/10 inch long).

About half the world's population lives in the hookworm belt

extending around the globe between 36° north and 30° south latitude. In this area, hookworms are one of the great retarding influences in community development, through their ill-effects.

Nature imposes fantastically complicated conditions on hookworms in their struggle for survival. They exist only where soil, moisture and temperature occur in the right combination. The soil must be sandy or loamy, not clay or muck. The rainfall must be more than 40 inches a year, and the mean annual temperature over 50°. On the other hand, the hookworm larva cannot survive long in water or sun.

The female hookworm in the human intestine lays from 5000 to 20,000 eggs a day, depending on her species. The host's daily bowel movement brings these eggs to earth, where under favourable conditions they hatch into rod-shaped larvae about 1/100 inch long. The larva feeds on bacteria, moults twice, almost doubles in size and becomes a thread-like worm which can now sustain life without food for as long as a month or more; when the ground is warm and wet, it is excitable and aggressive, and if by chance it comes into contact with the bare human skin it can bore through it like a corkscrew with surprising ease. Any contact of the human skin with hook-worm-infested soil suffices for infection to occur; when people walk bare-footed in the fields, the tender skin between the toes provides a preferred entry point into the human body. If it enters a lymphatic vessel, it is carried to the regional lymphnode where it is destroyed. If by chance it enters a blood vessel, it is carried alive via venous circulation to the right side of the heart and to the lungs. There in the alveolus or air sac where the blood absorbs inhaled oxygen, the worm makes another break and thence is pushed upwards by ciliary action via the bronchial tubes into the throat. Here it could be coughed out or swallowed. Once in the small intestine, the worm bites into the mucous membrane and establishes its residence. It drinks blood voraciously and matures. For its size, about half the length of a small pin, one adult worm can extract an amazing amount of its host's blood. If the person were not making new blood to replace this loss, from 150 to 1000 worms would bleed him dry in six months' time. According to an expert estimate, the human race's daily blood loss to hookworms is equivalent to bleeding 1,500,000 persons per day.

Anaemia is the primary consequence of hookworm disease. The infected person can readily make more blood if he has an adequate supply of iron in his diet. A person who is well fed and has an iron-rich diet can better withstand a hookworm attack than one who gets little to eat

and whose diet lacks iron. Hookworm disease reaches it highest frequency and severity in children in whom severe anaemia arrests both physical and mental development.

Italian physicians, in the 19th Century were the first to connect the worms with the disease. In Europe it was called "miners' anaemia", and the Italians showed that it could be diagnosed by showing in the feces the distinctive ova or eggs of the worms. In 1923 Dr. Norman Stoll perfected the technique of estimating how many worms a patient had from the number of hookworm eggs in one gram of his feces.

A German, Dr. Arthur Looss (1861—1923) parasitologist at the Government Medical School in Cairo, solved the mystery of how hookworm disease was transmitted. He accidentally spilled a hookworm culture on his hands and developed an itch and tiny sore. When he later found hookworm eggs in his faeces, he concluded that he had been infected *through the skin.* It took a few years for Looss's discovery to sink in. When it did, it revolutionised the method of control. Now the peril of *soil pollution* by defecation in the open fields, and of walking barefoot was recognized. An American Zoologist named Dr. Charles Wardell Stiles (1867—1941) tried to educate the American medical profession and the public about the menace of hookworm disease. Every lecture of his from 1892 to 1897 ended with these words: "Gentlemen, if you find cases of anemia in man in the tropics or subtropics, the cause of which is not clear to you, consider the possibility of hookworm disease, make a microscopic examination of the feces and look for eggs". He crusaded for provision of latrines and improvement of sanitation of homes, public schools and churches. As he said, a sanitary privy providing a safe disposal of excreta from rural homes was the key to prevention of hookworm disease. Treatment could cure many individuals, and thereby save their health at the time, but it could never stay ahead of new infections and reinfections as long as daily exposure to polluted soil prevailed.

Stiles had said that a human being wrecked by the "laziness bug" could be restored to health for 50 cents' worth of thymol and Epsom salts. However, the great drawback to thymol was that it often took not one but two or three and sometimes five or ten treatments to achieve a cure. This, with a purge before and after each time, left the patient weak and unwilling to come back for more. The drug caused nausea, headache and a burning sensation in the stomach in many patients.

Dr. Wilhelm Schuffner, a German physician had begun using oil of Chenopodium as a vermifuge in the Dutch East Indies as early as 1900 and by 1913 was able to report on the treatment of 100,000 cases. Oil of Chenopodium was cheaper and easier to administer and less unpleasant to take.

Maurice Hall, a Zoologist in U.S.A. in 1921 had noticed that animals anaesthetised with chloroform ($CHCl_3$) frequently expelled intestinal parasites afterwards, indicating that chloroform had a vermifuge action even when inhaled. Hall set about testing other hydrocarbons, finally hitting upon carbon tetrachloride (CCl_4). After trying it upon himself, Hall tried it successfully on a few monkeys without ill effects. In 1933 Dr. Lambert was able to report the treatment of 240,000 persons with CCl_4. But it caused occasional deaths especially in alcoholics. Maurice Hall in 1925 discovered that tetrachlorethylene (C_2Cl_4) was better and safer, and more acceptable to patients, a single dose given in gelatin capsule could knock out 90% of the patient's hookworms.

At present bephenium naphthoate is the best drug both for individual and for mass therapy. A single dose of 2.5g. of the base is usually effective.

Malaria

Malaria was well known to the ancients. Charaka and Sushruta gave vivid descriptions of the various types of malarial fever and associated it with the bites of mosquitoes. Hippocrates gave a classic description of malaria. In ancient Italy, people associated malaria with bad air, from which the name malaria is derived. The devastating effects of malaria have been described in the chapter on Fever (page 223). Medical historians believe that malaria had a great part in the downfall of Greek and Roman civilizations.

The modern scientific story of malaria began with Charles Laveran (1845—1922), a French Army Surgeon. In 1880, Laveran, while examining under the microscope the fresh blood of a malaria patient in Algeria, saw on his glass slide a spherical body with red pigment, which suddenly put out little whip-like hairs or flagellae.What he had observed we know now was the male form or gametocyte of malarial plasmodium in the first stage of sexual reproduction; the flagellae seek the female gametocyte and fertilize it so that it can spore within the mosquito.

The medical profession remained thoroughly skeptical of Laveran's findings until 1886, when Camillo Golgi (1844-1926), an Italian physician, confirmed it. Golgi also observed the plasmodium in a second non-sexual stage of multiplication, wherein it splits and releases new spores in the patient's blood stream. This stage, he showed, coincided with the paroxysm or chills soon followed by fever. At this time, there may be millions of spores in circulation.

The evidence that insects like mosquitoes carry germs of diseases was provided by Patrick Manson (1844—1922) who in the 1880's saw the filarial worm growing in the stomach of mosquitoes. Manson theorised that mosquitoes also were carriers of malaria parasite; not only that, but the mosquito acted as an intermediary host during a stage in which the parasite reproduced and developed in preparation to be spread back into the human host. Manson could not prove this theory; what he claimed sounded fuzzy and far-fetched. He was ridiculed as a crackpot, "mosquito-Manson". His critics queried whether infected mosquitoes got chills and fever.

Manson showed the "Laveran bodies" to Ronald Ross (1857 – 1932), a young British Army Surgeon, who had not been able to distinguish the plasmodia himself. In 1895 Ross returned to India and set out to test Manson's theory. He began by raising *culex* and *aedes* mosquitoes from larvae and fed them on patients with malaria. He then dissected the mosquito's stomach. He saw the malarial gametocytes put out their flagellae but nothing further. Next, Ross caused *culex* and *aedes* mosquitoes to feed on malaria patients and then bite healthy volunteers a few days later; no one got malaria. Ross was not an entomologist, and did not know there was such a thing as a spotted-winged *Anopheles* mosquito until he saw one in the hills near Ootacamund in the province of Madras. Ross wondered if he had perhaps been using the wrong mosquito. This was the turning point. In 1897 in a military barrack hospital in Trimulgiri near Secunderabad, Ross saw what happened when anopheles mosquito imbibed blood from a malaria patient; he saw cysts growing into the mosquito's stomach wall; these cysts contained pigmented malaria parasites. This discovery inspired him to write a poem in a letter to his wife, saying that he had found "thy cunning seeds,O,million-murdering death!" Switching to malaria in birds, as a more convenient research tool, Ross now working in Calcutta in 1898, showed that these seeds, emerging from ruptured cysts as rod-like spores, collected in the mosquito's salivary glands, and were secreted in saliva that wetted the insect's

proboscis as it jabbed it into the host's skin blood capillary. "Never in our dreams had we imagined such a wonderful tale as this," he wrote later. By 1898 Ross had demonstrated the entire life cycle of the parasite in bird malaria. In the same year, an Italian Giovanni Battista Grassi (1854—1925) along with his colleagues Bignami and Bastianelli, demonstrated the sporozoites of human malaria in the salivary glands of female anopheline mosquitoes. This led to an ugly controversy regarding the primacy of credit for the discovery—Ross or Grassi? Ross was knighted and received the Nobel Prize in 1902. Laveran received it in 1907. Golgi got it too, in 1906, not for his classic malaria work but for developing a staining method that enabled him to reveal the structure of brain and other nerve cells.

The new target of attack was the female anopheline mosquito. Between 1899 and 1902, Ross himself demonstrated the classic methods of mosquito control—drainage of the soil, oiling of stagnant pools, screening of buildings, isolation of persons with malaria and the regular use of mosquito nets over beds. Ross was much exasperated at the world's failure to exploit his discovery that the mosquito was to blame for malaria. He wrote: "I did not do this work on malaria in the interest of zoology, but in the interest of practical sanitation. Malaria could be completely eradicated through mosquito control".

The success of this approach was shown by Malcom Watson in a large number of plantations in Malaya, and by William C. Gorgas (1854—1920), a U.S. Army physician in the Panama Canal Zone during its construction from 1904 to 1914. His work was hailed as "the greatest sanitary achievement the world has ever seen". Men like Gorgas who act as links between discovery and its application need a combination of qualities as rare as those of the pure investigator.

In 1921 it was observed that Paris green (copper arsenic dust) was far superior to oil or anything else as a malaria mosquito larvicide. The stuff soon became the backbone of mosquito control and remained so until World War II. The amount floating on the water proved harmless to animals and fish.

In the middle 1930's, Paul Russel, an American expert and Dr. T. R. Rao, an Indian malariologist, tested the periodic spraying of houses in South India with *pyrethrum* (extracted from a daisy-like chrysanthemum), dissolved in kerosene. They found the method highly effective against Anopheles Culicifacies, and the method was welcomed by the villagers.

Dr. Fred Soper, achieved great success in Brazil in 1938 to 1940 and in Egypt in 1944-45, by vigilant measures to eradicate larvae of anopheles gambie by paris green and adult mosquitoes by pyrethrum spraying. In the application of scientific methods of eradication, he provided administrative efficiency and dynamic leadership.

Recapitulating "Lessons in Malariology from World War II", Russell commented that the decisive factor in controlling malaria in the armed forces was a *malaria conscious* command, which brought down malaria rates more than a year before DDT became available in practical amounts.

DDT was synthesized by Paul Muller (1899—1965) of the Geigy Company of Basel, Switzerland, as one of a series of related compounds in a search for new insecticides. Muller first tried DDT on flies; either in dust form or in spray it killed them in astounding numbers. Muller won the Nobel Prize in Medicine for his discovery, singularly because of one thing: he observed that DDT, wherever it fell, had a staying power, or *residual action,* not found in other insecticides like pyrethrum. DDT completely lacked the quick knock out power of pyrethrum. An insect coming in contact with DDT showed no effect for about twenty minutes; it then went into a drunken spin and fell to the floor, paralysed. It might not die for several hours. On the other hand, a dusted or sprayed surface remained lethal to insects landing on it for weeks and months, whereas pyrethrum killed only those present at the time it was sprayed.

The island of Sardinia, a rough, primitive island abounding in mountains and wide marshy plains, illiterate peasants, shepherds, had 75,000 cases of malaria in 1946. With DDT spraying the cases dropped to 44 in 1950. From 1951 to 1963 only ten new cases occurred. Much the same thing occurred in the rest of Italy too.

When the World Health Organization was formed in 1948, the first World Health Assembly placed malaria at the head of the list of health problems to which it gave priority. WHO defined malaria eradication as meaning a programme that in a limited time ended the transmission and eliminated the reservoir of malaria in a given population. Falciparum and vivax malaria die out in infected individuals within three years. Thus an eradication campaign must break the cycle of transmission for at least that time.

Few living creatures have developed a more uncertain survival method than the malarial plasmodia. The future of the plasmodia

depends upon the probability that through the large numbers of people with active malaria, of mosquitoes and of mosquito bites, the one-to-one chain will remain unbroken, and at times become greater than one-to-one when many mosquitoes bite one malaria patient. To avoid extinction the parasite produces hundreds of spores; the mosquito in turn lays hundreds of eggs. Overcreation is Nature's way of ensuring survival. Human inertia and sloppiness, aided by mutations causing breed of resistant strains of mosquitoes, are on the side of the plasmodium.

In 1955 when the 8th World Health Assembly recommended the eradication of malaria as an international objective, the initial expectation was that malaria would be eradicated in 5—10 years. Unfortunately this was not realised. There were major setbacks in the form of insecticide resistance in the vector, drug resistance in the parasite, and administrative, economic and political problems. Today malaria has been eradicated from the whole of Europe, most of North America including the whole of U.S.A., most of the Caribbean, large parts of northern and southern South America, Australia, Singapore, Japan, Korea & Taiwan. The position has unfortunately deteriorated in India and South-East Asia and Africa, and Turkey.

In India for ages malaria has been responsible for high *morbidity* and *mortality,* and the economic loss due to malaria in 1935 was estimated to be nearly Rs. 10,000 million per year. In April 1953 the National Malaria Control Programme (NMCP) was launched with residual insecticide (DDT) sprays. Two rounds of spray applied during the transmission season could effectively control malaria at a very reasonable cost. The programme proved highly successful. The incidence of malaria dropped down from 75 million cases in 1953 to 2 million cases in 1958. All aspects of life, agriculture and industry, showed improvement. This encouraged the conversion of control programme into a National Malaria Eradication Programme (NMEP) in 1958 with the goal of eradicating malaria from the country in the quickest possible time. The NMEP worked well till 1961, when a state of near-eradication was reached in vast parts of the country, with the lowest ever record of cases (49151) reached. From 1965 the programme suffered repeated setbacks with consequent rise in the number of parasite-positive cases, reaching 64 million in 1976, and still rising. The reasons for the setbacks are administrative, operational and technical. The administrative failures have been shortage of insecticides, shortage of manpower and shortage of finances. The operational failures have

been lack of sufficient transport, migration of labour population, habit of mud-plastering of houses and refusal of spraying on religious grounds. The technical hurdles have been the insecticide resistance in vector (twenty-four out of forty-two malaria-carrying mosquito species have become DDT-resistant), rocketting high prices of petroleum based insecticides (DDT from Rs. 3000 to 12000 per metric ton, malathion from Rs. 6000 to 16000 per metric ton).

The modified strategy since 1977 has been to prevent deaths due to malaria, selective spraying in "API 2 areas" (annual parasite incidence over 2%). The story of malaria is the story of lost opportunities.

Filariasis

The role of mosquitoes in the transmission of filariasis was recognized in the 1880's when Dr. Patrick Manson (1844-1922) found the thread-like worm of filaria growing in the stomach of mosquitoes that had fed on the blood of patients with this disease.

Approximately 236 million people in India are exposed to the risk of infection with filariasis. Unplanned urbanisation as part of a development programme seems to be rendering the ecological conditions in our country favourable for the breeding of mosquitoes and the spread of filariasis resulting in much ill-health and incapacitation. Pondicherry region is highly endemic for filariasis with a microfilaria carrier rate of 17.8 per cent in the general population. A research-cum-action oriented programme for the control of filariasis including the vector control has been launched by the ICMR's Vector Control Research Centre (VCRC), in close collaboration with the Government of Pondicherry. In view of the resistance of the culex mosquito vector to insecticides, alternative methods are being sought, such as attack on the larval stage by bio-environmental methods, and minor engineering methods to eliminate breeding places of the vector. The VCRC in Pondicherry has isolated a bacterial agent, Bacillus thuringiensis (serotype H-14) from the paddy field samples of the area, which acts as a potent biological control agent against mosquito larvae. Preliminary studies show good larvicidal action within 24 hours.

A new relatively inexpensive mosquito repellent with a long-lasting effect has been recently developed. This agent (N.Diethyl phenyl acetamide, Depa) can ward off mosquitoes for as long as 35 days, if sprayed on clothing. The compound is now undergoing clinical and toxicological trials at the Central Drug Research Institute (CDRI) at Lucknow.

The insecticidal and vermicidal action of fumigation were recognized by *Charaka Samhita* which has given several recipes for the purpose (Ci, 23, 98-100).

Extracts of three common plants viz. Ocimum sanctum and Ocimum bacillicum (two varieties of Tulasi) and Azadirachta indica (Neem) have been found to have larvicidal activity, particularly in combination with chemical insecticides. Culex larval control operations using these plants which grow abundantly in nature, may hopefully avoid aquatic environmental pollution by chemical insecticides.

Vector Control

During the latter part of the 19th Century and the early part of the 20th Century, the role of insect vectors in the transmission of several diseases was conclusively demonstrated. Methods for vector control included (1) personal protection i.e. screening and use of repellents; (2) habitat management and source reduction i.e. draining water sources and getting rid of artificial breeding sites; (3) the use of insecticides both as larvicidals and adulticides; (4) biological control by reducing larval number by fish etc. and (5) training and education of personnel. The public should realise the importance of vector control, and actively participate in it.

The development of residual insecticide during the 1940's presented a single method of vector control with an extremely high but incalculable cost-benefit ratio and became the major component of many vector control programmes. However, the development of resistance to insecticides in vectors, concern about environmental contamination and human safety and the increased cost of alternative insecticides led again to an emphasis on the development and use of several control techniques simultaneously or sequentially i.e. integrated vector control.

An adequate knowledge of the biology, ecology and behaviour of the vector and associated non-target organisms and of human behaviour must be applied to ensure not only effectiveness in controlling the vector but also human safety and prevention of other unacceptable side effects. Benefits should be recognizable and justify the costs involved.

Rise of Public Health Movement

Charaka, Sushruta and Hippocrates appreciated the influence of "airs, waters and places and seasons" on many important epidemic diseases.

In 1546, Fracastorius wrote "De Contagione" generally regarded as the first treatise on epidemiology. He studied syphilis, then a new

disease in Europe and postulated that a *contagium vivum* was the cause of some infectious diseases. His idea was based on the records of the epidemics in the community. He recognized the contagiousness of epidemic diseases such as typhus, and described the three methods of spread of "the causal agent" — by direct contact, by fomites or infected clothing or utensils, and at a distance as in smallpox and plague, what we consider today as droplet infection. The concept of vector-borne disease (mosquitoes, fleas, lice) was to come much later, although Charaka mentioned that epidemics occurred more frequently in the land abounding in *"mashak"* (mosquitoes), *"mooshaka"* (rats) and *"makshika"* (flies).

In 1662, Graunt collected data which showed the relation of age, sex, season and place to mortality from certain diseases. Thus the "unhealthiness of towns" (bowel and respiratory infections), of "country" (pellagra, mental deficiency), of "dangerous trades" (anthrax etc.), came to be appreciated.

In 1700 Bernardo Ramazzini, a Paduan professor, published the first book on occupational and industrial diseases. He described the respiratory illnesses of miners and stone masons which were created by dusts, and the lead poisoning of potters, and printers. Industrial diseases were to become a more pressing problem with the onset of the Industrial Revolution a century later. Even before this occurred, Ramazzini had drawn attention to the problem, and encouraged men to think of ways of prevention.

Johann Frank (1754 – 1821), a Viennese professor also waged a campaign to persuade rulers to care for the health of their subjects by the provision of efficient sanitation and water supply. Frank's radical belief that Governments should be responsible for public health was ahead of its time. The authorities were unconcerned and the impetus for change had to come from humane and dedicated individuals. Only in the army and prisons could hygiene and living conditions be controlled. Sir John Pringle (1707 – 1782), a physician to the British Army, was among the first to suspect that dirt might cause disease. To combat typhus, so common among armies, he tried to create in military hospitals effective hygiene, drainage and sanitation, and also experimented with "antiseptics", a word which he coined. His "Observations on the Diseases of the Army", proposing better ventilation in barracks, among other recommendations for soldiers' health, sold thousands of copies and was translated into French, German and Italian.

John Howard (1726 – 1790), the English prison reformer, recognized the association between typhus and dirt. At great personal risk and against the opposition of authorities, he conducted a tour of jails in England and Wales in the winter of 1773. Here he advocated the introduction of baths, soap and water, and the fumigation of clothes. His campaign produced results but the lessons were quickly forgotten and in the early 19th century James Neild and Elizabeth Fry had to fight the same battle again.

The Birth of Public Health

The birth of public health occurred in England around 1840. The evils of the industrial revolution on one hand, and the frequent visitations of cholera on the other, led to the rapid growth and development of public health movement in the western world. Filth was recognized as man's greatest enemy.

The idea that environment was an important source of illness had been evolving over more than a century. As early as 1719, when plague appeared again in Southern Europe, Richard Meade suggested not only more stringent application of traditional measures of isolation and quarantine, but also much wider improvements in the community; better housing, cleanliness, ventilation, disinfection, and control of nuisances. Perhaps the most significant work was Edwin Chadwick's publication in 1842, "Report on the Sanitary Conditions of Labouring Populations of Great Britain". This document examined the relation between environmental conditions and ill-health. By later standards much of the evidence was deficient; nevertheless it was a scientific epidemiological work. The effectiveness of hygienic measures became meaningful from the time Pasteur established the bacterial origin of infectious diseases. Microbiology was of course the source of preventive and therapeutic measures applied to the individual; but it also contributed powerfully to the advances in hygiene which were even more important for the community, for example by showing how infection is spread, and making it possible to identify specific diseases, including their unsuspected presence in "carriers". Hygienic measures were responsible for at least a fifth of the reduction of the death rates between the mid-19th century and today. This is the proportion of the decline which was associated with water and food-borne diseases.

By the use of simple statistics, public health reformers brought home the relationship between poverty, living conditions, socio-economic status and mortality rates. A good illustrative example is provided by

the following study of H. Gavin in 1848.

No. of deaths	*Area* *Bethnel Green (1839)*	*Average age of diseased*
101	Gentlemen and families	45
273	Tradesmen and families	26
1258	Servants, labourers & families	16

By such studies the epidemiologists identify the distribution of disease, the pattern of its occurrence, the factors that determine the patterns, and particularly how the factors can be modified to eliminate the disease from the population. An epidemiologist is a public health detective who searches for causes and ways to prevent them.

Uses of Epidemiology

By the epidemiological approach, medical science learned about nutritional deficiences and their causes (Lind— scurvy; Takaki—beri-beri; Goldberger—pellagra). The harmful effects of overnutrition and obesity were also established by epidemiological approach (actuarial data on premature mortality from cardiovascular disease among the overweight). Environmental factors causing malignant disease have also been discovered by the epidemiological approach (cancer of scrotum in chimney sweepers; cancer of bladder in aniline dye workers; cancer of cervix and penile hygiene; leukemia and radiation). The relationship of tobacco smoking and various diseases is discussed in an earlier chapter. It is interesting to note that causes and their prevention can be found long before the exact mechanism is understood (e.g. Lind's discovery of prevention of scurvy by fresh lemons, Pott's discovery of chimney sweeper's cancer,or Snow's discovery of cholera prevention). In most cases eventually experimental verification is obtained to confirm the hypothesis. But some times epidemiology remains as the only crucial evidence when clinical observations are ambiguous and no experimental model is available for verification of the hypothesis.

Epidemiology is the study of disease and its distribution in defined populations. The hallmark of epidemiology is the concern with the identification of both the individuals who have the disease under study and with enumerating those who do not. In this way it is possible to calculate *rates* of occurrence of disease and to estimate whether the

disease is commoner in people with particular characteristics than in others, whether it is commoner in one place than another, and whether the occurrence has changed over time.

Several general measures are commonly used in epidemiology. The *incidence* of a disease is the number of *new* cases occurring during a specified period of time. The incidence rate is this number per specified unit of population, say per thousand or per 100,000 or per million. The *prevalence* of a disease is the *total* number of cases of the disease existing in the population at a specified time. The prevalence rate is this number expressed per unit population. In circumstances where the incidence of a disease and its duration — length of time from onset to recovery or death — remain constant over time, the prevalence of the disease equals the product of its incidence and duration.

The main application of epidemiology has been to study the determinants of the distribution and spread of disease in populations. The aim is to identify factors which are causally associated with the occurrence of disease and which may be manipulated to prevent the disease.

The concept of *causal association* is one of profound importance in epidemiology. First, an observed association may be causal (factor A causes disease B) either directly or indirectly, such that a change in the factor will result in a change in the frequency of the disease. Secondly, the possibility must be considered that the disease has caused the factor associated with it, rather than vice versa, as when the occurrence of the disease itself leads to a change in say, the dietary, behavioral or physiological variables under study. Thirdly, an observed association may be non-causal. For example, if factor A influences both factor B and disease C, then factor B and disease C will be associated statistically. However, the association between B and C being non-causal, there would be no hope of producing a change in disease C by manipulating factor B. Awareness of the possibility of obtaining spurious associations, through "confounding" variables, is a central feature in the design, analysis and interpretation of epidemiological studies.

Despite the major advances that have occurred in medicine, there are still many diseases for which there is no cure and where immediate hope for the future lies in prevention, the fundamental principles of which may sometimes be far removed from medical therapeutics and prophylaxis.

Chapter 21

PROMOTION OF POSITIVE HEALTH AND PREVENTION OF DISEASE

Introduction

When the World Health Organization was set up in 1948, we were encouraged to think in terms of positive health and to measure it on a scale that culminated in "Complete physical, mental and social well-being". Positive health remains, however, elusive to quantify and we still have to measure the impact of our work by the extent to which we have succeeded in preventing, curing and relieving disease, including in this term injuries and medical disabilities of all kinds.

In this sense, the approach of Ayurveda is very comprehensive indeed. The aim of Ayurveda is to promote health — *"Swasthasya Swasthya Rakshanam"*, increase immunity and resistance — *"Vyadhi Kshamatva"*—and to cure disease—*"Aturasya Vyadhi Parimokshana"*.

The concept of drugs and practices that increase resistance to disease — *Vyadhikshamatva,* is very attractive. But it is a difficult task to validate the claims of such practices unless there are objective, quantifiable parameters of *"bala"* and *"oja"* (strength and energy) which are alleged to be increased. The same comment applies to rejuvenation therapy of the elderly.

Our major emphasis therefore, has to be on prevention of disease. The success of smallpox eradication shows that if scientific evidence of preventability is clear, it is possible to surmount bureaucratic inertia, deep-rooted prejudices, careless indifference and economic barriers to eradicate a disease.

The lessons learned and the tools developed during the smallpox experience also point the way to the eventual control of the most rapidly growing epidemics of our times, those of *man-made diseases*, that is, those diseases which would not have occurred if human beings had not interfered with their environment. Examples:—

(1) *Toxic substances in the environment:* (Such as asbestos in the factory, sulphur dioxide in the air over a city, insecticides in rural areas, volatile agents inhaled with cigarette smoking or incompletely tested drugs such as Thalidomide, whether they act as simple toxins or as carcinogens, teratogens or mutagens). (2) *Gamma ray, X-ray and other harmful radiations.* (3) *Accidents* in man-made environment, (such as crushing injuries from machines without safeguards, reckless driving of automobiles, fires in households and godowns).

There are 600,000 chemicals in India, many of them man-made, in the atmosphere, affecting human health adversely, through water, air and soil pollution. Since the measures taken to control pollution are limited due to high cost, many people are exposed to skin diseases, eye irritation, chronic respiratory disease and cancer. The major harmful pollutants in the atmosphere are sulphur dioxide, hydro-carbons, carbon monoxide, carbon dioxide, oxides of nitrogen, ozone and benzpyrine. According to Dr. Rashmi Mayur, who has been crusading against environmental pollution in India for the last several years, approximately 1700 tons of these pollutants are dumped in the environment of Bombay city each day. Almost 80 per cent of the 430 million gallons of sewage going untreated into the sea is destroying marine life and reducing the ocean's capacity to process carbon dioxide. Massive deforestation upsets the ecological balance.

The Bhopal tragedy in December, 1984, wherein leakage of methyl isocyanate and phosgene from the Union Carbide pesticide plant took an unprecedented toll of over 2000 human lives and thousands of animals, is a solemn reminder of the duty of industry and Government in protecting the population from atmospheric pollution.

Sir Richard Doll, in his Harveian Oration of 1982 on 'Prospects for Prevention', has listed the opportunities for prevention under the following seven broad heads.

1. Socioeconomic improvements
2. Modification of personal habits
    - Smoking
    - Use of alcohol and addictive drugs
    - Diet
    - Physical exercise
3. Protection against trauma
4. Control of infection
5. Control of pollution

6. Population screening
    Antenatal
    Postnatal
7. Prophylactic Medication

Periodic Health Examination

Charaka Samhita makes the following observation:

"The ignorant man fails from stupidity or negligence to note the incipient state of a disease, just as a simpleton fails to recognize a potential enemy".

"Disease, from atomic beginnings assumes enormous proportions. Therefore before even diseases show themselves or while yet they are in the incipient stage, one who cares for one's happiness should endeavour to have them treated with proper medication".

In recent years a great deal of interest has arisen in the concept of periodic health check-up, of asymptomatic people. The periodic health examination has two main goals: the prevention of specific diseases and the promotion of positive health. Most of the detection manoeuvres customarily employed in the periodic health check-up are included because they have been helpful diagnostic adjuncts in the *symptomatic patient.* It does not necessarily follow that they would be as useful in the detection of *pre-symptomatic* disease or in the detection of *risk status* for a particular disease.

The Canadian Task Force on the Periodic Health Examination was established in 1976 to determine how the periodic health examination might enhance or protect the health of the population. Their report is the most rigorous, detailed and comprehensive evaluation of the periodic health examination to date.

Many questions have to be answered in relation to periodic health check-up.

1. Does early detection of the disease or risk factor lead to a better outcome among those who follow the subsequent health advice?
2. Does early detection of a condition or risk factor benefit those to whom it is offered?
3. Is the effective manoeuvre being made available to those who could benefit from it with optimal use of resources?
4. If today's detection test for curable cancer gives a negative result, how soon should the test be repeated?

The appropriate intervals between detection attempts may differ

widely from disorder to disorder, as well as the natural history of each of the pertinent disorders.

We should start by identifying the main killing or disabling conditions, unhealthy states and unhealthy behaviours prevailing in our society and then determine which ones could possibly be prevented according to present knowledge, by encouraging preventive measures and health-promoting practices. Based on current knowledge, various age and sex-specific health protection packages can be offered, with special consideration for the pre-natal, childhood and advanced age phases of human life. Certain stages of life such as birth, school entry and retirement are mandatory check-points for health examination of the entire population.

The current burden of suffering is assessed by two factors: (1) the impact of the particular condition on the individual as assessed by *the years of life lost, the amount of disability, pain and discomfort,* the cost of treatment and the effect on the individual's family, (2) the impact on society as assessed from mortality, morbidity and the cost of treatment.

The value of immunization in health protection has been established for many conditions. The value of nutritional supplements and vitamins has also been established in the case of pregnant women and children. It would be important to *identify preventable conditions* pertaining to each age group and to assess the detection manoeuvres and preventive interventions related to each condition. The Canadian Task Force recommendations are reproduced here in full because of their usefulness.

Table I gives alphabetical list of conditions reviewed by the task force.

Table II summarizes the effectiveness of prevention and treatment, the quality of evidence regarding effectiveness of interventions, and the classification of recommendations as under:

Grading of effectiveness of intervention according to the quality of evidence.

I. Evidence obtained from at least one properly randomized controlled trial.

II.1 Evidence obtained from well-designed cohort or case-control analytic studies preferably from more than one Centre or research group.

II.2 Evidence obtained from comparisons between times or places with or without intervention.

III. Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Classification of recommendations:

A. There is *good* evidence to support the recommendation that the condition be specifically considered in a periodic health examination (PHE)
B. There is *fair* evidence to support the recommendation.
C. There is *poor* evidence regarding the inclusion of the condition in a periodic health examination and recommendations may be made on other grounds.
D. There is fair evidence to support the recommendation to exclude the condition from consideration in a PHE.
E. There is good evidence to support the recommendation that the condition be excluded from consideration in a PHE.

The concept of health maintenance over a person's entire life is important. This needs health education and counselling and its implementation through alteration of unhealthy states of behaviour such as smoking or the failure to use car seat belts or scooter head protection helmets, which are determinants of ill health, disability and untimely death.

According to a newer concept of family practice, the family doctor assumes responsibility for a defined population, and therefore has better opportunities of imparting health education and alter public attitudes and health behaviour, better health surveillance, disease prevention and early detection of treatable diseases.

Just as a car insurance company gives "no claim bonus" as an incentive for safe driving, incentives are needed for encouraging health protection and disease prevention.

A Practical Approach to Preventive Medicine

Despite the obvious common-sense proposition that preventing illness is good not only for health but also for the pocket, we have relegated prevention to a very low rank on the national health priority list. In the last century preventive measures were introduced against communicable diseases and have been by and large accepted. More recent efforts to introduce preventive measures for non-communicable diseases have been far less successful, in areas such as cigarette smoking, obesity, hyperlipidemia, hypertension and alcoholism, and accident prevention.

A Lifetime Health Monitoring Programme incorporates prevention into day-to-day care, and helps to strengthen the patient-doctor relationship.

The family physician should ensure, for different age groups of his families-under-care, various targets to be fulfilled. For instance, during infancy: seven immunizations, tests to detect anaemia, haemorrhagic diseases, phenyl ketonuria and developmental deficiencies, and routine prophylaxis for gonorrhoeal ophthalmia. In the age group 40 to 59: tests for hypertension, cervical, mammary, oropharyngeal and gastro-intestinal cancer, and control of obesity and smoking are in order.

Even when preventive procedures are compulsory as for childhood immunizations, non-compliance is substantial. Making the entire programme compulsory would be neither feasible nor acceptable. It may be more practical to offer *financial incentives.* Perhaps it may be possible to impose some sort of *financial penalty* for failure to participate, or reward for doing so, as in the case of family planning.

In the ultimate analysis, the crucial determinant is public attitude. Education, by definition is the method to modify or alter behaviour, hence health education is the ultimate instrument. The wisdom of Ayurveda lies in recognition of this fact and the incorporation of health conduct rules *("Swastha Vritta")* in the body of Ayurveda. What we need today is a modern version of Ayurvedic Swastha Vritta.

TABLE I

Alphabetical listing of preventable conditions reviewed by the Canadian task force.

Accidents (other than motor vehicle accidents) (71)
Acute gastroenteritis of childhood (19)
Alcohol consumption (37)
Alpha-1-antitrypsin deficiency (47)
Ankylosing spondylitis (73)
Bacteriuria in pregnancy (66)
Blood group incompatibility in pregnancy (62)
Cancer of the bladder (54)
Cancer of the breast (48)
Cancer of the cervix (49)
Cancer of the colon and rectum (50)
Cancer of the lung (bronchogenic carcinoma) (51)
Cancer of the oral cavity (57)
Cancer of the prostate (53)
Cancer of the skin (55)

Cancer of the stomach (52)
Chlamydial genital infection (26)
Cholelithiasis (76)
Chronic bronchitis (46)
Congenital dislocation of the hip (7)
Congenital syphilis (3)
Consequences in children of parents with alcoholism (14)
Cystic fibrosis (9)
Dental caries (67)
Diabetes mellitus in the nonpregnant adult (58)
Down's syndrome (13)
Duchenne muscular dystrophy (10)
Family dysfunction and marital and sexual problems (34)
Gonorrhoea (24)
Hearing impairment (40)
Hemolytic streptococcal infection resulting in
acute glomerulonephritis or acute rheumatic
fever (20)
Hemorrhagic disease of the newborn (2)
Herpesvirus type 2 and cytomegalovirus infection (27)
Hodgkin's disease (56)
Hyperactivity and learning disability (33)
Hyperlipidemia (42)
Hypertension (43)
Hyperthyroidism (59)
Hypothyroidism (60)
Immunizable conditions related to international travel (smallpox,
cholera, yellow fever, typhus, plague, typhoid and hepatitis) (16)
Immunizable infectious diseases (15)
Interventricular septal defect (11)
Iron-deficiency anemia (45)
Low birth weight (28)
Malnutrition (29)
Menopause (61)
Motor vehicle accidents (70)
Neonatal hypothyroidism (5)
Neural tube defect (8)
Obesity in childhood (30)
Ophthalmia neonatorum (gonococcal) (4)
Orthodontic conditions (68)

Other immunizable conditions (18)
Parasitic diseases, excluding toxoplasmosis (23)
Parenting problems, including child abuse and neglect (32)
Periodontal disease (69)
Peptic ulcer (75)
Phenylketonuria (6)
Postnatal asphyxia (1)
Preterm labour (64)
Primary open-angle glaucoma (41)
Problems of physical growth (hormonal) (31)
Progressive incapacity with ageing (78)
Psychiatric disorders (affective disorders and suicide) (35)
Recurrent spontaneous abortion (65)
Refractive defects (39)
Retirement distress (77)
Rheumatoid arthritis (74)
Scoliosis (72)
Smoking (36)
Strabismus (38)
Syphilis (25)
Tay-Sachs' disease (12)
Thalassemia (44)
Toxoplasmosis (22)
Tuberculosis (17)
Urinary tract infection (21)
Unwanted teenage pregnancy (63)

Author's Note: One important disease should be added to the above list: leprosy (see page 446 of this book); prospects of using leprosy vaccine to protect population at risk for developing lepromatous leprosy in India, are bright. By early case-finding and chemotherapy, deformities are entirely preventable.

Preventive healthcare is a dynamic, evolving discipline. As new therapies and preventive strategies are developed, preventive services must be reassessed and changes in healthcare packages recommended.

TABLE II

Summary of effectiveness of prevention and treatment, quality of evidence, manoeuvres and recommendations relating to 78 conditions studied by the task force.

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
1. Postnatal asphyxia	Prevention: fair	II-1	Detection during pregnancy of causative factors suggesting high risk. Fetal monitoring during labour.	B
2. Hemorrhagic disease of the newborn	Prevention: effective	II-2	Vitamin K1, 1 mg after birth.	B
3. Congenital syphilis	Prevention: usually secondary since mother infected Treatment: penicillin before 16th week usually effective.	II-2	Serologic testing	B For general population A For high risk group

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
4. Ophthalmia neonatorum (gonococcal)	Prevention: effective	II-1	Instillation of 1% silver nitrate solution into each eye.	A	
5. Neonatal hypothyroidism	Efficacy of screening for case finding is excellent. Diagnosis in infancy improves mental prognosis Treatment: highly effective.	II-1	Thyroxine testing with filter paper in all neonates; ancillary spot testing for thyroid stimulating hormone if necessary.	A	Recall serum thyroxine tests may be used as aids when necessary High-risk group: infants whose mothers have taken iodides, propylthiouracil or radioactive iodine
6. Phenylketonuria	Screening and treatment are highly effective if performed between 4 and 21 days of life.	II-1	For detection, microbiologic inhibition (Guthrie) and fluorometric tests; may need repeating and supplementing with paper chromatography.	A	Since screening of newborns under 4 days of age may result in underreferral, a second test is justifiable

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
7. Congenital dislocation of hip	Screening and/or case finding detects cases in time to allow corrective treatment	II-2	Clinical examination (flexion, abduction and Ortolani manoeuvre); confirmation by roentgenography.	B
8. Neural tube defect	Primary prevention may imply abortion; hard to assess effectiveness and efficacy. In pregnancies tested, about 80% of open neural tube defects are detected	II-1	Maternal serum alphafetoprotein testing; with elevated values, supplement with ultrasonography and amniocentesis.	B Screening should be available to pregnant women on request if parents understand that confirmation of result may require ultrasonography and amniocentesis, and are prepared to accept therapeutic abortion if the fetus is affected.

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
9. Cystic fibrosis	Prevention secondary or tertiary. Early treatment increases survival and is associated with better prognosis.	II-2	Detection: iontophoresis sweat test on at least two occasions, and observation for clinical signs.	D For general population B For high-risk group; siblings of cystic fibrosis patients
10. Duchenne muscular dystrophy (DMD)*	Prevention: probably effective in identified carriers. Treatment: poor	III	Serum creatine phosphokinase determination	C For general population B For high-risk group; female relatives of DMD patients
11. Interventricular septal defect (VSD)	Treatment by surgical closure of VSD effective	II-2	History taking and clinical examination; chest roentgenography, echocardiography and cardiac catheterization for confirmation	B High-risk factors; positive family history, certain chromosomal disorders, rubella during pregnancy, low birth weight, prematurity and diabetic mother

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
12. Tay-Sachs' disease	Prevention: effective Treatment: ineffective	II-1	Measurement of resistance of serum hexosaminidase to heat inactivation; amniocentesis as confirmatory test	D B	For general population For high-risk group; includes Ashkenazi Jews
13. Down's syndrome	Prevention: effective, but identification of women at risk is relatively poor. Treatment: none	II-1	Elicit information on patient's history; if positive, amniocentesis only if parents are prepared to accept abortion when it is indicated.	D B	For general population For high-risk groups; parents with translocation of chromosome 21, or family history of Down's syndrome and mothers over 35 years of age.
14. Consequence in children of parents with alcoholism	Counselling effective in reducing both amount of drinking in pregnant women and morbidity in their offspring.	II-2	Counselling to reduce alcohol intake; contraception for alcoholic, sexually active women; abortion, if acceptable, for pregnant women at high risk	B	

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
15. Immunizable Infectious diseases					
Diphtheria	Prevention: good	I	Immunization of persons in good health	A	Adult dose after 6 years of age
Measles	Prevention: good	I	Immuniztion of persons in good health	A	Vaccine is contra-indicated in children with a history of convulsions and pregnant women; caution is advised in persons allergic to egg protein
Mumps	Prevention: Good	I	Immunization of persons in good health	A	Vaccine is contra-indicated in pregnant women, persons allergic to neomycin and persons suffering from altered immune status; caution is advised in persons allergic to egg protein

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
Pertussis	Prevention: good	I	Immunization of persons in good health	A	Contraindication: family or personal history of convulsions. Immunization not recommended after 6 years of age.
Poliomyelitis	Prevention: good	I	Immunization of persons in good health	A	In certain circumstances (e.g., immunodeficiency) it is better to use inactivated poliomyelitis vaccine (Salk) instead of oral vaccine (Sabin) Contraindications: treatment with corticosteroids or antileukemic drugs, neurologic

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
18. Other immunizable conditions:				
Influenza	Vaccine is efficacious	I	Immunization	E For general population A For high-risk groups: persons 65 years of age or older and those with chronic debilitating disease Contraindication: allergy to egg protein
Pneumococcal pneumonia	Vaccine is efficacious against 80% of pneumococcal infections	I	Immunization	E For general population A For high-risk groups: persons with chronic debilitating illness, sickle-cell anemia or asplenia. Do not

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
				revaccinate before 3 years. Vaccine should be avoided in children younger than 2 years; effects on the fetus are unknown.
Meningococcal meningitis	Vaccine is efficacious; immunity ranges from a few months to 3 years depending on vaccine	I	Immunization	E For general population A For high-risk groups: military recruits and travellers in infected countries Serogroup C vaccine should be avoided in children younger than 2 years; effects of vaccine on the fetus are unknown

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
19. Acute gastroenteritis of childhood	Prevention: anecdotal evidence for efficacy of breast-feeding; Treatment: effective in infants whose condition is not otherwise adversely affected	II-2	Oral rehydration therapy	D Serious illness usually occurs in infants under 2 years of age; its expression tends to be influenced by socio-economic as well as nutritional factors
20. Hemolytic streptococcal infection resulting in acute glomerulonephritis or acute rheumatic fever	Secondary prevention effective in communities under certain conditions	General population screening: I High-risk groups: III	Elicit history of exposure to betahemolytic streptococcal infection: throat culture.	E For general population C For high-risk groups
21. Urinary tract infection	Screening detects some cases, but yield is low Reinfection often follows treatment	II-2	Urinalysis	D

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
22. Toxoplasmosis	Hygienic measures effective	III	Elicit information on exposure; serologic testing for *Toxoplasma gondii* and counselling on hygiene for high risk group	C For general population A For high-risk group nonimmune pregnant women who keep a cat at home or eat raw meat
23. Parasitic diseases, excluding toxoplasmosis	Hygienic measures effective	III	Stool examination	C For high-risk group for inspection with *Ascaris lumbricoides* and *Giardia lamblia*
24. Gonorrhoea	Prevention: limited Treatment: effective	II-2	Smears of cervix and urethra and cultures of cervical and urethral secretions and of first-voided urine.	D For general population A Pregnant women should be examined A For high-risk group: persons with a history of multiple sexual partners

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
25 Syphilis	Prevention: limited effectiveness Treatment: efficacious if given early	II-2	Various blood tests	D For general population A For pregnant women A For high-risk group; persons with a history of multiple sexual partners
26 Chlamydial genital infection	Prevention: difficult Treatment: antibiotics	III	Blood tests, cultures smears	C
27 Herpesvirus type 2 and cytomegalovirus infection	Prevention: unknown Treatment: none efficacious	III	Blood tests, cultures and microscopy	C
28 Low birth weight	Prevention: adequate diet by mother (especially proteins) efficacious; abstinence from smoking advised	II-2	Ensure adequacy of protein and energy intake; advise mother to abstain from or reduce smoking	B

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
29. Malnutrition	Prevention: uncertain Treatment: fair	III	History taking, height and weight measurement and other anthropometric measurements and determination of serum protein concentration for high-risk groups	C B	For general population For high-risk groups: adolescent girls, pregnant women, those nursing for unusually long periods, food "faddists"
30. Obesity in childhood	Evidence for effectiveness of prevention and treatment is lacking	III	Accurate serial measurements of height and weight	C	
31. Problems of physical growth (hormonal)	Treatment: effective and efficacious for short stature due to hypothyroidism, hypopituitarism and congenital adrenal hyperplasia	II-2	Serial measurements of height and weight and other anthropometric measurements	B	Research priority

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
32. Parenting problems, including child abuse and neglect	Intervention may be effective in preventing child abuse	Child abuse: II-1 Parenting: III	Appropriate taking, counselling and assessment of parent-child interaction	A Child abuse C Parenting Research priority
33. Hyperactivity and learning disability	Prevention: ineffective Treatment: efficacious for hyperactivity	Hyper-activity: I Learning disability: II-2	Assess parent-child interaction; preschool educational screening	C For both conditions Research priority
34. Family dysfunction and marital and sexual problems	Uncertain	III	History taking and counselling	C Research priority
35. Psychiatric disorders (affective disorders and suicide)	For psychotic effective disorders treatment is efficacious For neurotic or reactive affective disorders treatment is of uncertain efficacy. For suicide the value of prevention not shown	I II-1 II-2	No predictive manoeuvre is available	D For all conditions Research priority

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
36. Smoking	Counselling efficacious rather than effective	Efficacy: II-1 & II-2 Effectiveness: III	History taking and counselling	C High-risk groups: women taking oral contraceptives, diabetics, individuals with hypertension and/or elevated blood cholesterol concentration, persons with evidence of disease attributable to smoking, workers in asbestos, silica, uranium, coal and grain industries Research priority
37. Alcohol Consumption	Prevention: not yet effective Treatment: efficacious to some degree	III	History taking and counselling	C Research priority

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
38. Strabismus	Secondary prevention of amblyopia effective	II-1	Simple inspection and cover-uncover test	B Research priority
39. Refractive defects	Prevention: not possible Treatment: effective	III	Visual acuity testing	C Research priority
40. Hearing impairment	Prevention: ineffective Treatment: some benefits from remedial therapy	II-2	History taking and clinical examination	B Individuals who warrant further study include: – infants whose parents suspect a defect, who fail to react to a novel noise outside their field of vision or – who manifest decreased or absent "babbling", – children with retarded or defective speech development

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
					– adults with hardness of hearing or who fail to respond to the normal spoken voice. Research Priority
41. Primary open-angle glaucoma	Early treatment prevents symptomatic visual loss	III	Funduscopy, visual field testing and measurement of intraocular pressure	C	Research priority
42. Hyperlipidemia	Unclear	III	Taking family history in young male and determining serum cholesterol and triglyceride concentrations	C	
43. Hypertension	Prevention: not possible Treatment: efficacious	I	Blood pressure measurement;	A	Labelling to be avoided unless

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
			evaluation and treatment as appropriate		treatment and prolonged follow-up are planned
44. Thalassemia	Unknown	III	History taking, laboratory screening and counselling	C	For general population
				B	For Asian, African and Mediterranean people of parenting age Since assistance to carriers is not available, members of the high-risk group should be asked whether they want to participate in screening,

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
				having first been informed of the pertinent facts Research priority
45 Iron-deficiency	Prevention: possible Treatment: will raise hemoglobin concentration but value unclear	III	Determination of blood hemoglobin concentration and MCHC	C High-risk groups; premature babies, babies born of a multiple pregnancy or an iron-deficient woman, and persons in low social-economic circumstances
46. Chronic bronchitis	Prevention: abstinence from smoking is associated with absence or lower frequency of airway obstruction and low respiratory disease mortality	II-1	Encourage abstinence from smoking	D

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
	Treatment: cessation of smoking is effective.				
47. Alpha-1-antitrypsin deficiency	Prevention and treatment: unclear	II-1	Encourage abstinence from smoking	D	
48. Cancer of the breast	Mortality in women aged 50 to 59 years is lowered by early detection through physical examination and mammography	I	For women aged 50 to 59 years: annual mammography and physical examination of the breast	A	Research priority
49. Cancer of the cervix	Prevention and treatment: efficacious	II-1	Papanicolaou smear	B	For all sexually active women at least every 3 years upto age 35 and every 5 years thereafter. For high-risk groups (early age of sexual

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
					activity and/or variety of sexual partners) smears should be taken at least annually Research priority
50. Cancer of the colon and rectum	Prevention: fair, some evidence of secondary prevention through screening using sigmoidoscopy Treatment: fair with early surgical treatment in presymptomatic phase	I and II-2	Testing stool for occult blood	B	High-risk groups; persons with history of colitis, familial polyposis or villous adenomas, or family history of cancer of the colon Research priority
51. Cancer of the lung (bronchogenic carcinoma)	Prevention: abstinence from smoking efficacious	II-1	None validated	D	Research priority
52. Cancer of the stomach	Some evidence of value of secondary prevention	II-1	Photofluorography, saline wash and	C	

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
	through screening using endoscopy, photofluorography and gastric cytologic analysis		cytologic examination of gastric contents, and examination of stool for occult blood.	
53. Cancer of the prostate	Prevention and treatment no evidence of efficaciousness at present	III	Digital palpation per rectum, prostatic massage and cytologic examination, and determination of serum acid phosphatase concentration	C
54. Cancer of the bladder	Prevention: unknown Treatment: fair	III II-1	Cytologic analysis of urine	D For genral population B For high-risk groups: workers occupationally exposed to bladder carcinogens and smokers

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
55. Cancer of the skin	Prevention: unknown Treatment: effective	II-1	Counselling and inspection	D For general population B For high-risk groups: outdoor workers and those in contact with polycyclic aromatic hydrocarbons
56. Hodgkin's disease	Prevention: ineffective Treatment: relatively effective	III	Physical examination and roentgenography	C
57. Cancer of the oral cavity	Prevention: unknown; early detection is possible, but effect on outcome is unclear Treatment: depends on site of lesion	Early detection: III Effectiveness of ensuing treatment II-1	Visual examination	C Males and all smokers are at increased risk. Early diagnosis is enhanced by the toluidine blue test, cytologic examination and/or biopsy

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
				when indicated by clinical inspection
58. Diabetes mellitus in the non-pregnant adult	Treatment of asymptomatic persons has not been shown to be effective in controlling complications	I, II-2	Urine testing for glucose, and fasting and post-cibal blood glucose tests	D For general population B High-risk factors: family history of diabetes, abnormalities associated with pregnancy and physical abnormalities such as circulatory dysfunction and frank vascular impairment
59. Hyperthyroidism	Treatment is effective, but therapy in asymptomatic phase is not necessary	II-2	Measurement of serum thyroxine and triiodothyronine concentrations and	D

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
			thyroid binding globulin saturation index	
60. Hypothyroidism	Treatment of clinical hypothyroidism is effective	III	Clinical examination in postmenopausal women	C Research priority
61. Menopause	Prevention: Impractical since women in whom vasomotor symptoms will develop cannot be identified Treatment (of hot flushes, vaginal dryness and mood disturbances): effective	III	Measurement of plasma estradiol concentration	C
62. Blood group incompatibility in pregnancy	Both high when Rh hyperimmune globulin given to Rh-negative women	I	Blood group and anti-body test	A

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
63. Unwanted teenage pregnancy	Little evidence for prevention of first pregnancy	III	Counselling on contraceptive use and follow-up; abortion	C
	Good evidence for prevention of second pregnancy	I		A
64. Preterm labour	For incompetence of cervix; fair	II-2	Elicit previous history; cerclage of cervix	B Research priority
	For other causes of preterm labour; further study required	III	Elicit previous history; pharmacologic treatment; delivery in specialized centre	C
65. Recurrent Spontaneous abortion	Potential causative factors are identifiable in 30% of cases, but not all are amenable to treatment	III	Investigation to detect possible cause of problem	C
66. Bacteriuria in pregnancy	Secondary and tertiary prevention: effective Treatment:	II-1	Microbiologic examination of urine	B

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
	long-term effectiveness not established			
67. Dental caries	Both prevention and treatment give excellent results	Topical application of fluoride: I Water fluori-dation: II-1 Dietary couns-elling: II-2 Secondary preventive measures: III Regular check-up	Visual and tactile examination and roentgenography if appropriate	C Those at highest risk are between ages 3 and 20 years
			Fluoride application for residents of areas without fluoridated water supply; water fluoridation	A Research priority

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre		Recommendations and comments
		III Frequency of check-up: III			
68. Orthodontic conditions	Both prevention and treatment can give excellent results	Early detection II-2 Treatment II-2	Oral examination and roentgenography	B	Research priority
69. Periodontal disease	Prevention and treatment: unclear	Efficacy of preventive measures: III Frequency of exami-nation: III	Visual and tactile examination and encouragement of daily oral hygiene	C	Research priority
70. Motor vehicle accidents	Unclear: seat belts and helmets	III	Control of underlying medical conditions,	C	Special attention should be given

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
			counselling of disabled, and encouraging the use of seat belts by all drivers and passengers	to persons at high-risk because of physical defects or impairment
71. Accidents (other than motor vehicle accidents)	No evidence available	Cannot be assessed	Use periodic health examinations scheduled for other purposes to encourage safety in the home and the community	C An important proportion of accidents occur at home, where young children and the elderly are particularly at risk
72. Scoliosis	Unknown	III	Physical inspection of schools by nurses	C
73. Ankylosing spondylitis	Both are of limited effectiveness	III	Detection of individuals with HLA-B27 antigen	C
74. Rheumatoid arthritis	Prevention: unknown Treatment: fair	III	Unclear	C

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
75. Peptic ulcer	Prevention: no available means Treatment: efficacious	II-2	Elicit history	D
76. Cholelithiasis	Chenodeoxycholic acid is efficacious for primary and secondary prevention for limited periods; its effectiveness has not been studied	III	For primary prevention, duodenal drainage of bile (limited use); for secondary prevention, oral cholecystography± duodenal drainage	C
77. Retirement distress	Prevention: effective but largely psychologic	III	Final counselling before retirement as part of a series of periodic health examinations throughout adulthood	C
78. Progressive incapacity with ageing	Detection of undeclared health conditions and correction of unsuitable living conditions:	II-2	Enquiry by healthcare professional into physical, psychologic and social competence,	B

Condition	Effectiveness of prevention and treatment	Quality of evidence	Manoeuvre	Recommendations and comments
	effective		conducted in the home, with organ-system enquiry and further action if indicated	

Basis for research priority*

	Condition	Priority	Comments
31.	Problems of physical growth (hormonal)	+ +	To determine the optimal frequency of height and weight measurements
32.	Parenting problems including child abuse and neglect	+ + +	To identify specific manoeuvres that would be effective in assessing and treating parenting problems
33.	Hyperactivity and learning disability	+ +	To detemine the specificity and sensitivity of the measuring instruments, the groups of risk for learning disorders and the effectiveness of early intervention for these groups
34.	Family dysfunction and marital sexual problems	+	To determine the effectiveness of prevention

	Condition	Priority	Comments
35.	Psychiatric disorders (effective disorders and suicide)	+	To determine if enquiry during a periodic health examination about depression and suicidal ideas followed by treatment of identified cases does more good than harm
36.	Smoking	+	To establish the effectiveness of counselling as a means of cessation and, if not satisfactory, research into better methods of compliance with abstinence from smoking
37.	Alcohol consumption	+	To determine if counselling has any effect in reducing alcohol consumption
38.	Strabismus	+	To determine the optimal frequency of examination
39.	Refractive defects	+ +	To determine the value of presymptomatic detection of refractive defects
40.	Hearing impairment	+	To determine the value of early detection and of detection strategies available
41.	Primary open-angle glaucoma	+ +	To obtain data on the epidemiology and natural history of the various types of glaucoma, the effectiveness of treatment and the magnitude of long-term compliance among patients, the ability of various types of health care providers to perform optic disc examination, and the appropriate screening periods for different age groups and persons with and without ocular hypertension

	Condition	Priority	Comments
44.	Thalassemia	+	To determine the effectiveness of prevention
48.	Cancer of the breast	+ + +	To determine the separate benefits of mammography and clinical examination, and the optimal frequency of these manoeuvres, the benefits in age groups other than sixth decade, especially the fifth, the risk of harm from irradiation by current techniques, compliance in a non-selected population, the specific benefit of breast self-examination and the advantage of employing allied health professionals in screening programmes.
49.	Cancer of the cervix	+	To determine the optimal age and frequency for taking Papanicolaou smears
50.	Cancer of the colon and rectum	+ +	To determine the sensitivity, specificity, acceptability, side effects and appropriate frequency for simple detection manoeuvres such as testing the stool for occult blood since grade I evidence for the effectiveness of preventive manoeuvres applies only to sigmoidoscopy
51.	Cancer of the lung (bronchogenic carcinoma)	+	To determine the effectiveness of existing strategies against smoking and, if not satisfactory, research into better methods of obtaining compliance with abstinence from smoking.

	Condition	Priority	Comments
60.	Hypothyroidism	+ +	To obtain evidence that treating subclinical or biomedical hypothyroidism alters the clinical course.
64.	Preterm labour	+	To determine how to identify women at risk and the effectiveness of the treatments currently used.
67.	Dental caries	+	To determine the optimal frequency of examination
68.	Orthodontic conditions	+	To determine the optimal frequency of examination
69.	Periodontal disease	+	To determine the optimal frequency of examination and the effectiveness of counselling on oral hygiene

* + = research priority; + + = high research priority; + + + = high and urgent research priority

EPILOGUE

The World Health Organization has defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity." This definition emphasizes that our attitude towards health should be a positive one. Unfortunately in our thinking about health heavy reliance is placed on negative indices—mortality, morbidity and disability in measuring the health status of communities. We hardly ever talk in terms of positive indices of health.

A unique feature of Ayurveda is its emphasis on the promotion of positive health, and its prescription to attain positive physical, mental and social health by a regime of *Swastha Vrutta* (healthy conduct) and *Sad Vrutta* (ethical conduct). The following advice by Charaka sums up the whole concept beautifully.

Nityam Hitaharavihara Sevee, Samikshyakari Vishayetwasakthah
Datha, Samah, Satyaparah, Kshamawan, Aptopasevee Bhavet Arogah

"He alone can remain healthy, who takes regulated diet and exercise, who deliberates all his actions, who controls his sensual pleasures, who is generous, just, truthful and forgiving, and who can get along with his kinsmen."

It is essential to impart health education to people so that they recognize their personal responsibility and obligation for maintaining health and working positively to attain it.

In the long term, better health will depend on socio-economic progress, environmental improvement and the spread of education, including health education.

The Alma Ata Conference on Primary Health Care (September, 1978) called upon the commitment of governments and societies to the achievement of primary health care for all citizens in all countries of the world. It is hoped that by this approach there would be better

health for everybody by the year 2000 A.D.

Of the nearly six and a half billion people to be cared for by 2000 A.D. over four and a half billion will be citizens of the developing world. The poorest 30 percent of the world population will be in Asia and Africa. About 800 million people today are desperately poor. It has to be clearly understood that the health of the absolutely poor can only be improved by relieving their poverty which in turn means providing *full employment.*

Rudolf Virchow, a medical luminary in the mid-nineteenth century had proclaimed that the right of citizens to work was a fundamental principle to be included in the constitution of a democratic state. Virchow understood, as we his successors have not, that medicine if it is to improve the health of the public, must attend at one and the same time to its biologic *and* to its social underpinnings. "The improvement of medicine will eventually prolong human life, but the improvement of social conditions can achieve this result more rapidly and more successfully."

The health of the people is a matter of direct social concern. Social and economic conditions have an important effect on health and disease. The measures taken to promote health and to combat disease must be social as well as medical. It is paradoxical that at the very moment when the scientific prowess of medicine has reached unprecedented heights, our neglect of the social roots Virchow so clearly identified cripples our effectiveness. In Virchow's words, "Medical instruction does not exist to provide individuals with an opportunity of learning how to earn a living but in order to make possible the protection of the public."

Benjamin Disraeli, Prime Minister of England during a parliamentary debate on the Public Health Act of 1875 had said, "Public health is the foundation on which repose the happiness of the people and the power of a country. The care of people's health is the first duty of a statesman". Judging by these words, one is forced to conclude that many statesmen in the world today are badly educated, or not statesmen at all. In our age the greatest challenge before world medicine is to see that the most useful parts of the knowledge we already have are brought to all those who need it.

The essential ingredients of primary health care, are listed below:

1. Adequate food and nutrition.
2. Adequate supply of safe drinking water.

3. Basic sanitation including provision of latrines.
4. Housing.
5. Maternity and child care, including family planning.
6. Immunization against major infectious diseases.
7. Appropriate treatment of common diseases and injuries at low cost—with special emphasis on malaria, tuberculosis and respiratory infections, leprosy, gastro-intestinal infections & worm load; prevention of deficiency of iron, iodine, Vit.A.
8. Health education.

It is evident that any failure in achieving these objectives will not be due to lack of scientific knowledge but due to lack of commitment and political will, and lack of efficient administrative action. No one can dispute that these are the primary health care priorities. It is worth emphasizing that in these areas *our success or failure will have nothing to do with our faith in a particular system of medicine.* It is curiously perverse, even dishonest to argue that alternative medicine is needed because modern medicine has failed to deliver the goods.

At present, in most developing countries, three quarters of the people still live in villages, yet three quarters of the health expenditure is usually in towns. As a result of such pattern of expenditure, majority of the people in the villages and urban slums have no access to organized health services. It is surely no accident that one of the most famous and original medical books of the decade, "Where there is no doctor", by David Werner, a biologist, required such an imaginative leap in the medical care of the disadvantaged, that no doctor could write it.

Forty per cent of the world's population lives in China and India. The spectacular Chinese achievements in the last thirty years in land reforms, in food production and distribution, and in public health should inspire India to do likewise. A very important national health programme has started in India in 1980, covering 150 community blocks (roughly a quarter of the population). The integrated child development service (ICDS) scheme provides a package of services to children upto six years of age, pregnant women and lactating mothers; services include immunization, nutrition supplement (300 additional kilocalories, 15 grams of protein, iron, folic acid and Vitamin A), nutrition for severely malnourished children, health check up, antenatal services, post-natal care, pre-school education, informal adult education of women, and health and nutrition education. All services

are delivered at a central point in each village (''anganwadi'') by a local village woman specially trained for this purpose. In many parts of India more than half of the children die before the age of five from a lethal combination of malnutrition and infectious diseases suceptible to simple interventions well within the capacity of the most basic health care services. Until infant and child mortality falls parents are unlikely to be interested in spacing or limiting their families.

Every right-minded Indian, medical or non-medical, should consider himself or herself as having a stake in the success of this endeavour, and its extension to the whole country. The task is so stupendous that *all* available medical and paramedical manpower in the country should be harnessed; their education and training should be based on scientific principles, which have been illustrated throughout this book.

Poverty, hunger, malnutrition and communicable diseases will be eliminated before long from the developing countries, as they have been eliminated from the affluent world. But what about another kind of poverty, to which Mother Teresa pointedly drew the attention of her affluent Western audiences? Are not the achievements of eliminating infant mortality nullified by the rising tide of teenagers' deaths by automobile accidents, homicide and suicide?

The mental and social health of many affluent countries does not appear to be at its best, as shown by several indices— alcoholism, drug addiction, crimes of a wide range including rape, assaults, robbery and homicide, suicide, increasing divorce rates, unwanted teen-age pregnancy and so on. In the ultimate analysis all these are behavioral disorders and maladaptive responses to a stress-ridden life. ''The mind'', said John Milton,'' is its own place and in itself can make a heaven of hell and a hell of heaven.''

The World Health Organization has recently come out with a statement that Nuclear War will be an irremediable disaster. In the past the human propensity to warfare could only produce limited damage, but now such disorders of human behaviour will put the whole planet in jeopardy. Today when global defence expenditure is $450 billion each year or about a million dollars a minute, and when close to half of the scientists and engineers work for military, wasting an enormous potential of human ingenuity and creativity by developing ever more sophisticated means of total destruction, the teachings of Buddha and Mahatma Gandhi become all the more relevant in today's world. All wars begin in the minds of men; so also the quest for peace begins there.

Ancient Indians gave deep thought to the mind and spirit. Great stress was laid on mind-control or *"Chitta-Vritti-nirodha"*. Adding an ethical and moral dimension to health is a unique approach of Ayurveda. Twentieth-Century biology leaves out any consideration of the "Spirit" which is boldly tackled by Ayurveda. In the wise words of Weiszacker "The physical view of the world is not wrong in what it asserts, but in what it leaves out."

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